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Transition Metal-Free Approach to Propynenitriles and 3-Chloropropenenitriles

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Abstract: A transition metal-free, facile and efficient one-pot protocol for the synthesis of propynenitriles from readily available 3-chloropropenals is disclosed. The reaction conditions have also been optimized for the exclusive formation and isolation of 3-chloropropenenitriles which are important building blocks in general and are intermediates in the synthesis of propynenitriles. The hallmark of the methodology is the use of non-toxic reagents, milder, metal-free and economically benign reaction conditions avoiding a harsh dehydration step while achieving excellent yields.

Keywords: aqueous ammonia; chloropropenenitriles; iodine; propynenitriles; transition metal-free conditions

Propynenitriles **1** as well as 3-chloropropenenitriles **2** are versatile synthons in organic chemistry for the synthesis of a plethora of heterocyclic motifs associated with interesting chemical and biological properties (Figure 1).[1] Furthermore, the chemistry of variously substituted acetylenes has undergone a renaissance in the past decade as the carbon-carbon triple bond of alkynes is one of the constitutional functional groups in organic chemistry exhibiting fundamental reactions of synthetic utility.[2] On the other hand, the cyano group has always been envisaged as a fountainhead of functionalization in organic medicinal chemistry due to its facile transformation to functional groups of medicinal significance such as amines, amides, amidines, aldehydes, ketones, carboxylic acids, esters etc., many of which have already been used as its bioisosteres. The combination of these two versatile functionalities, viz. alkyne and cyano, in alkynenitriles make these as much sought after intermediates of potential synthetic as well as medicinal importance.

Surprisingly, there is only one method available in literature for the synthesis of 3-chloropropenenitriles **2** through a three-step process utilizing acetophenones as starting material [Eq. (1), Scheme 1].[3] There have

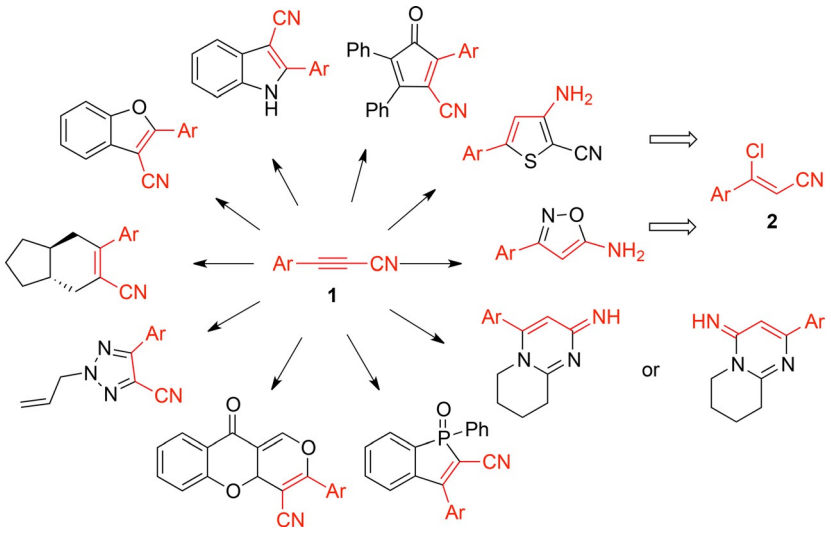
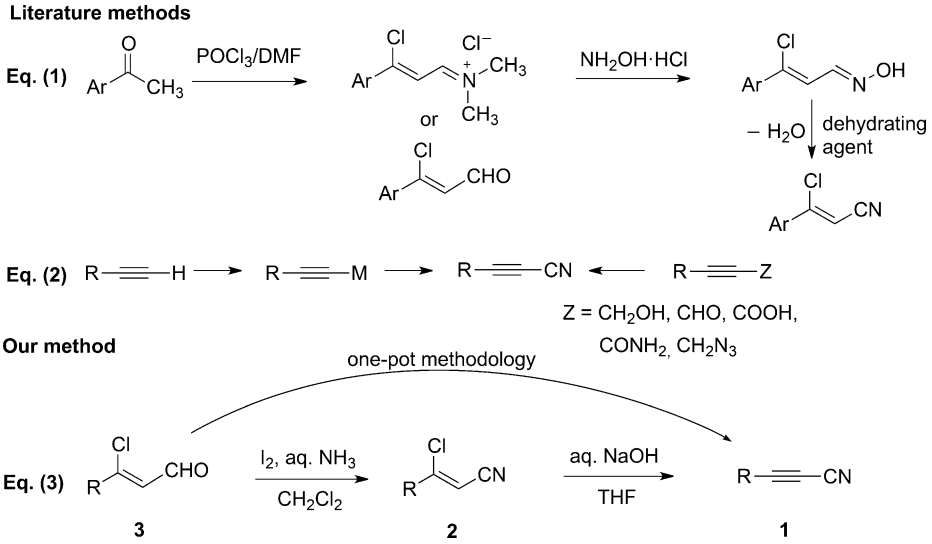


Figure 1. Synthetic applications of propynenitriles and 3-chloropropenenitriles.



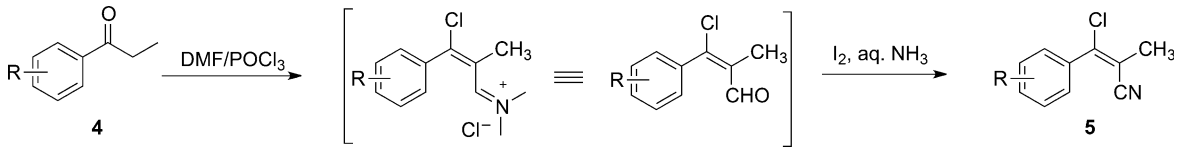
Scheme 1. Synthetic routes for 3-chloropropenenitriles and propynenitriles.

been slight variations to this three-step process by way of changing the dehydration reagent from trichlorophosphate to acetic anhydride,[4] attempting it as a one-pot process[5] or achieving the synthesis by a continuous flow method.[6] A fundamental strategy employed widely for the preparation of alkynenitriles **1** involves introduction of a cyano group to the terminal alkyne *via* metal acetylide and using cyanating agents such as cyanogen bromide,[7] cyanogen iodide,[8] cuprous cyanide,[9] 1-cyanobenzotriazole,[10] phenyl cyanate,[11] 1-cyanoimidazole,[12] and 2-pyridyl cyanate[13] [Eq. (2), Scheme 1]. The transformation of a functional group such as aldehyde, alcohol, amide, azide, etc. already present in the alkyne into nitrile is the other important strategy to prepare alkynenitriles [Eq. (2), Scheme 1].[14] However, all these protocols often require harsh reaction conditions, toxic reagents such as dehydrating and cyanating agents and are neither economic nor eco-friendly. Herein, we report a simple, facile and transition metal-free approach for the synthesis of both propynenitriles **1** and 3-chloropropenenitriles **2** starting from 3-chloropropenals **3** [Eq. (3), Scheme 1].

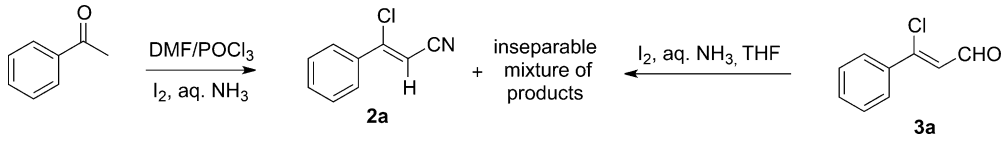
Recently, Togo and co-workers[15] reported a simple one-pot conversion of propiophenones **4** to the corresponding propenenitriles (β-chloro-α-methylcinnamonitriles) **5** (Scheme 2). Surprisingly, the authors neither included any acetophenone (a simple acetyl derivative other than propiophenone) in the study nor offered any explanation or clue for negating the obvious choice of acetophenones. It was interesting as well as intriguing on one hand to ponder upon the choice of authors not to include acetophenones in the study, on the other hand it was tempting to find an answer to this question by investigating the fate of acetophenones under the reaction conditions used by Togo and co-workers[15] for converting propiophenones to **5**.

In our investigation for extending the scope of the above methodology to acetophenones, we treated acetophenone under their reaction conditions.[15] Unfortunately, the expected 3-chloropropenitrile was not obtained as a single or major isolable product, instead a gummy mass indicating a mixture of products on TLC was obtained. Repeated purification of the mixture by column chromatography led to the isolation of a tiny amount of the predominant product as 3-chloropropenenitrile **2a** (Scheme 3).

Isolation of an insignificant amount of 3-chloropropenenitrile **2a**, in line with the conversion of propiophenones to **5** (Scheme 2), reaffirmed our notion that this methodology is also applicable to acetophenones but the presence of a proton, rather than a methyl group, at the α-position to nitrile is responsible for side reactions leading to the mixture of products. It also confirmed that formation of a mixture of products and isolation of the required 3-chloropropenenitriles in a very poor yield might have forced Togo and



Scheme 2.

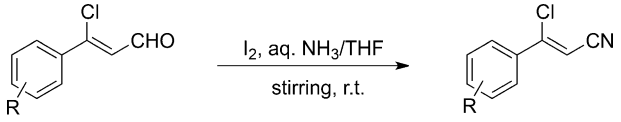


Scheme 3.

co-workers[15] to limit their investigations to propiophenones. In our next attempt to explore the possibility of driving the reaction in favour of exclusive formation of 3-chloropropenenitrile **2a**, we first isolated 3-chloropropenal **3a**, an intermediate in line with the conversion of propiophenones to β-chloro-α-methylcinnamonitriles, and treated it with iodine (1 equiv.) and aqueous ammonia in THF which again led to the formation of a mixture of products with 3-chloro-3-phenylpropenenitrile **2a** as the predominating product on TLC; this reinforced our belief that it is the second step in the process which is responsible for the side reactions when propiophenone is replaced by acetophenone. Next, we envisaged to investigate the effect of substituents and temperature in order to explore the possibility of driving the reaction towards exclusive conversion of 3-chloropropenal **3a** to **2a** (Table 1). In general, a mixture of products was obtained in most cases, however, to our surprise, exclusive formation of the 3-chloropropenenitriles was observed in the case of 3-chloro-3-phenylpropenals having *p*-methoxy (**3c**, entry 3) or *p*-fluoro (**3d**, entry 4) substituents. Lowering the reaction temperature to −15 °C resulted in the exclusive formation of 3-chloropropenentirile in another case involving a *p*-bromo substituent (**3f**, entry 6) while a mixture of products was obtained in all other cases (Table 1). It is worth mentioning that controlled addition of a solution of iodine (1 equiv.) in THF over a period of 10–12 h at −15 °C could control the reaction to some extent and led to isolation of 3-chloropropenenitrile **2** as a single product in all cases except for *p*-nitro (**3g**, entry 7) and *m*-nitro (**3j**, entry 10) substituents. These observations led us to conclude that electronic effects play a great role in controlling the reaction course thus giving a mixture of products in the case of substrates having electron-withdrawing groups. As the nitro group is the strongest electron-withdrawing group, the reaction could not be controlled even at −15 °C in the case of substrates **3g** and **3j**.

Considering the significance of electronic effects, next we investigated the effect of different solvents on this reaction. As the nitro substituent was found to be the most difficult for controlling the reaction, a solvent study was carried out taking 3-chloro-3-(4-nitrophenyl)propenal **3g** as the starting material. Accordingly, the reaction of **3g** with molecular iodine (1 equiv.) and aqueous ammonia at room temperature for 3 h was carried out in various solvents which are compatible for using the iodine/aqueous ammonia system (see Table S1 in the Supporting Information). Although a mixture of products was observed on TLC in THF, ethyl acetate, acetonitrile, DMSO and 1,4-dioxane, it was satisfying to note that no side reactions were observed while using chloroform (entry 7 of Table S1, Supporting Information) or dichloromethane (entry 8 of Table S1, Supporting Information) as solvent leading to the exclusive formation of **2g**. More importantly, the reaction was completely reproducible in both these solvents and there was no need for controlling either the temperature or the rate of addition of iodine. Reaction in *p*-xylene (entry 4 of Table S1, Supportting Information) also controlled the side reactions as evident from TLC but the reaction did not go to completion even after 10 h at room temperature. These observations led us to conclude that solvents having low water miscibility were efficient in controlling the side reactions. Optimization of reaction time led us to use dichloromethane as solvent as the reaction was completed in 45 min (entry 10 of Table S1, Supporting Information) and pure **2g** could be isolated in 87% yield. The reaction under these conditions can also be monitored visually as consumption of iodine, indicated by decolourization of the original violet colour, signifies the com-

Table 1. Substituent and temperature study.

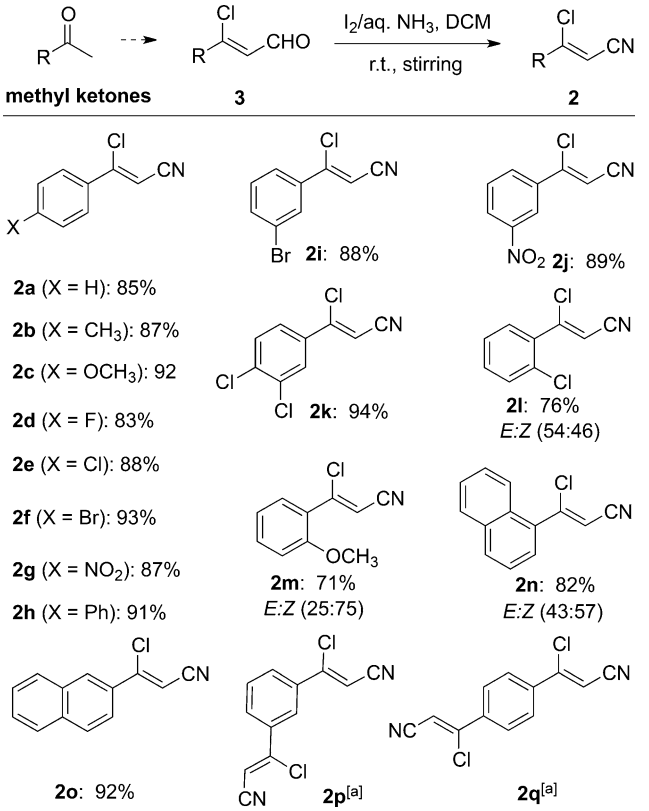


3a–3j **2a–2j**

Entry	**3**, R	Product (Yield) at: r.t./3 h	−15 °C/3 h	−15 °C/10–12 h
1	**3a**, H	mixture[a]	mixture[a]	**2a** (78%)
2	**3b**, *p*-CH_3	mixture[a]	mixture[a]	**2b** (81%)
3	**3c**, *p*-OCH_3	**2c** (89%)	**2c** (91%)	**2c** (90%)
4	**3d**, *p*-F	**2d** (78%)	**2d** (80%)	**2d** (80%)
5	**3e**, *p*-Cl	mixture[a]	mixture[a]	**2e** (77%)
6	**3f**, *p*-Br	mixture[a]	**2f**	**2f** (75%)
7	**3g**, *p*-NO_2	mixture[a]	mixture[a]	mixture[a]
8	**3h**, *p*-Ph	mixture[a]	mixture[a]	**2h** (83%)
9	**3h**, *m*-Br	mixture[a]	mixture[a]	**2i** (82%)
10	**3j**, *m*-NO_2	mixture[a]	mixture[a]	mixture[a]

[a] As visible on TLC, mixture could not be identified.

Table 2. Substrate scope for 3-chloropropenenitriles.



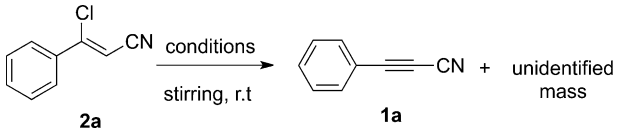
[a] 2 equiv. of iodine were used.

plete conversion of chloropropenal **3g** to chloroacrylonitrile **2g**.

Having the optimized reaction conditions in hand, we explored the substrate scope and successfully synthesized seventeen differently substituted 3-chloroacrylonitriles (Table 2). It is pertinent to mention here that only *Z*-isomers of alkenes were obtained except for the methyl ketones substituted with 2-chlorophenyl **2l**, 2-methoxyphenyl **2m** and 1-naphthyl **2n** groups where both *E* and *Z* forms were obtained in 54:46, 25:75 and 43:57 ratios, respectively, as measured by ^{1}H NMR. Two compounds, **2p** and **2q**, having double chloropropenenitrile functionalities were found to be too unstable to be isolated and characterized although they could be further transformed to propynenitriles **1p** and **1q** by a one-pot methodology (see Table 4).

Successful development of this new methodology for the conversion of acetophenones to chloroacrylonitriles *via* chloropropenals allows us to reflect upon the difference in behaviour of propiophenones and acetophenones and also paves our way to synthesize propynenitriles. It seems that under basic conditions, a trigger for the side reactions is the abstraction of an alkene proton either at the propenal stage or at the propenenitrile stage that is more likely in polar water-miscible solvents than in relatively non-polar water-immiscible solvents. Furthermore, as we were precisely focused on examining the mechanism of reaction of 3-chloropropenals with molecular iodine and aqueous ammonia in THF as solvent leading to the formation of a mixture of products, it was intriguing to know the fate of 3-chloropropenals either with molecular iodine under neutral conditions or with molecular iodine under ammonia-free basic conditions (to avoid the formation of aldimine and hence the nitrile) by employing sodium hydroxide, sodium bicarbonate, triethylamine, piperidine and pyridine. Either of these conditions failed to give a reaction which led us to conclude that 3-chloropropenal is first converted to 3-chloropropenenitrile followed by abstraction of the α-proton to the nitrile under basic conditions leading to the formation of a mixture of products. Next we envisaged to react 3-chloropropenenitrile **2a** with molecular iodine alone as well as with molecular iodine under basic conditions using different bases including aqueous ammonia (Table 3). Again, a mixture of products (entry 1) was formed in the presence of iodine and aqueous ammonia. Surprisingly, a single product was seen on TLC plate when **2a** was treated with molecular iodine and aqueous sodium hydroxide (1 equiv.) at room temperature for 3 h leading to complete consumption of reactant **2a** as evident from TLC of the reaction mixture (entry 2). The single product formed was isolated and identified as 3-phenylpropynenitrile **1a** on the basis of its spectral data. 3-Phenylpropynenitrile **1a** was also formed as a single product when **2a** was treated with molecular iodine and aqueous sodium bicarbonate but the reaction was incomplete after 3 h (entry 3). No reaction occurred

Table 3. Reaction of 3-chloro-3-phenylpropenenitrile (**3a**) with different bases.



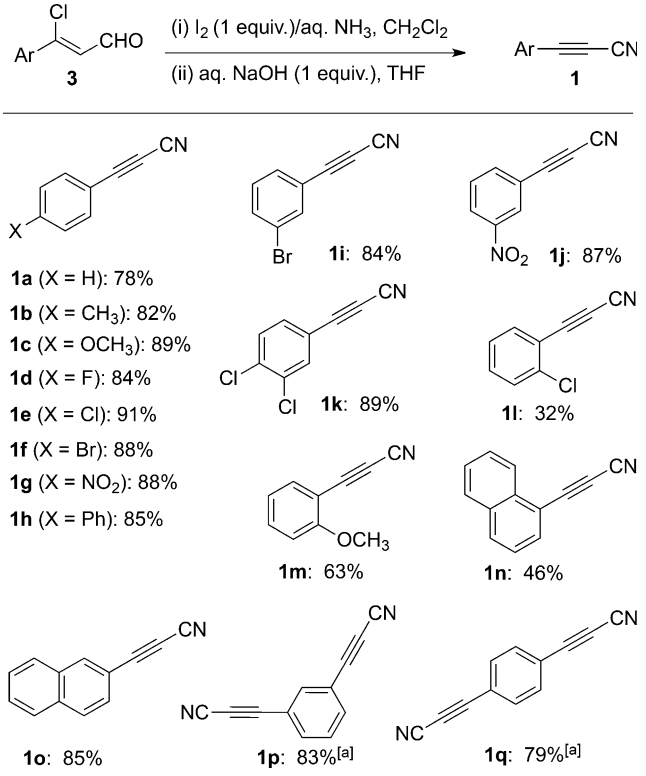
Entry	Reagents	Time	Product(s)
1.	I_2 (1 equiv.) + aq. ammonia	3 h	mixture
2.	I_2 (1 equiv.) + aq. NaOH (1 equiv.)	3 h	**1a**
3.	I_2 (1 equiv.) + aq. $NaHCO_3$ (1 equiv.)	3 h	**1a**, incomplete reaction
4.	I_2 (1 equiv.) + TEA (1 equiv.)	3 h	no reaction
5.	I_2 (1 equiv.) + pyridine (1 equiv.)	3 h	no reaction
6.	I_2 (1 equiv.) + piperidine (1 equiv.)	3 h	no reaction
7.	aq. ammonia	3 h	mixture
8.	aq. NaOH (1 equiv.)	3 h	**1a**
9.	aq. NaOH (1 equiv.)	15 min	**1a**

when TEA, pyridine or piperidine were used along with molecular iodine (entries 4, 5 and 6). Next we carried out the reaction of **2a** with aqueous ammonia without using iodine and the same mixture of products (as in case of entry 1) was obtained (entry 7) but using aqueous NaOH solution alone again led to the formation of **1a** exclusively (entry 8). The reaction time was then optimized and it was found that reaction takes just 15 min for complete conversion of 3-chloropropenenitrile to propynenitrile. These results validated our assumption that the reaction of 3-chloro-3-phenylpropenal (**3a**) with I_2 and NH_3 first leads to the formation of 3-chloro-3-phenylpropenenitrile (**2a**) which further reacts under the reaction conditions to give a mixture of products including 3-phenylpropynenitrile (**1a**). Thus, in this study, we successfully identified another component of the mixture of products obtained on treatment of 3-phenyl-3-chloropropenal with molecular iodine and aqueous ammonia in THF and also developed the methodology for the preparation of propynenitriles **1**.

Finally, the two-step conversion of 3-chloropropenals to propynenitrile was achieved in a one-pot manner by concentrating the reaction mixture through evaporation of the solvent of the first step on a rotary evaporator and treating the residual mass as such with aqueous NaOH in THF. After optimization of the protocol for the one-pot preparation of propynenitrile from 3-chloropropenals, we synthesized seventeen differently substituted propynenitriles (Table 4). It is noteworthy to mention here that when differently substituted arylchloropropenenitriles were subjected under the basic conditions, only *Z*-isomers of alkenes underwent elimination reaction leading to the formation of corresponding propynenitriles while *E*-isomers were not converted to propynenitriles and remained as such. Since replacing the aromatic ring by *o*-Cl-phenyl, *o*-OCH_3-phenyl and 1-naphthyl led to formation of both *E* and *Z* isomers of chloropropenenitriles, mixtures of propynenitriles and unreacted *E*-isomer of chloropropenenitrile were obtained in all these three cases. The mechanism of elimination reaction leading to the formation of propynenitriles **1** is given in the Supporting Information (Scheme S1).

In summary, we have established an efficient one-pot protocol to synthesize propynenitriles from 3-chloropropenals *via* 3-chloropropenenitriles employing mild aqueous reaction conditions. The methodology is featured by use of non-toxic reagents, milder, metal-free and economically benign aqueous reaction conditions avoiding a harsh dehydration step while achieving excellent yields. Furthermore, the chloropropenenitrile as well as propynenitriles (except **1l**, **1m** and **1n** which were separated from their corresponding *E*-chloropropenenitriles left unreacted by chromatography) obtained after simple work-up are sufficiently pure thus negating the need for flash chromatography.

Table 4. One-pot methodology for propynenitriles.



[a] 2 equiv. of iodine were used.

Experimental Section

Typical Experimental Procedure for the Conversion of β-Chloropropenals 3 into 3-Chloropropenenitriles 2

To a solution of 3-chloropropenal (**3**, 1.00 mmol) in 10 mL of dichloromethane under stirring was added molecular iodine (1.00 mmol) in one lot. 2 mL of 30% aqueous ammonia solution were then added and reaction mixture was allowed to stir further. The violet colour of iodine started to fade and the solution became almost colourless in 45 min indicating complete consumption of iodine. Aqueous sodium thiosulfate solution was then added in order to neutralize excess iodine if any, and the organic layer was separated, washed 2–3 times with water, dried (fused $CaCl_2$) and finally dichloromethane was evaporated under reduced pressure to afford pure β-chlorocinnamonitrile **2**.

Typical Experimental Procedure for One-Pot Conversion of β-Chloropropenals 3 into Propynenitriles 1

To a stirring solution of 3-chloropropenal (**3**, 1.00 mmol) in 10 mL of dichloromethane was added molecular iodine (1.00 mmol) followed by addition of 2 mL of 30% aqueous ammonia solution. The reaction mixture was allowed to stir

further for 45 min when whole solution became almost colourless showing the complete consumption of iodine. Excess of iodine was neutralized with aqueous sodium thiosulfate solution and the organic layer was evaporated under reduced pressure. THF was then added to dissolve the solid mass left followed by addition of aqueous NaOH solution. The reaction mixture was further allowed to stir for 15 min. when the TLC showed complete consumption of reactant. The whole reaction mixture was then added to water and the resulting solid was filtered off, dried and recrystallized from a mixture of ethyl acetate and petroleum ether.

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