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WATER ASSISTED AND CHOLINE CHLORIDE-DIMETHYLUREA DEEP EUTECTIC SALTS AS CATALYST TOWARDS THE ATTRACTIVE REACTION OF INDOLE, BENZALDEHYDE, AND MALONONITRILE

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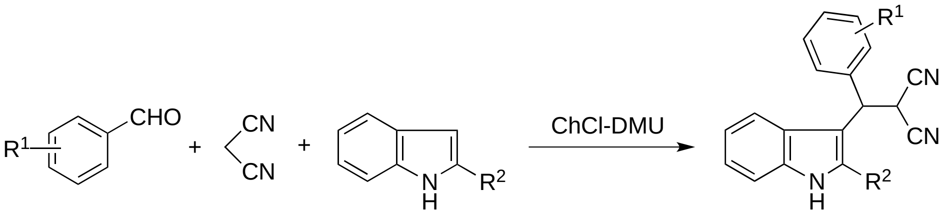
Abstract – The condensation of indole, benzaldehyde, and malononitrile was relatively rigorous compared with other Yonemitsu type reaction. We described a strategy using catalytic amount of choline chloride-dimethylurea deep eutectic salts as cheap and safe accelerator. We also found that introducing right amount of water in reaction system was crucial. This method tolerates variations in all three components to get desired 3-substituted indoles in satisfactory yields.

Yonemitsu condensation which was first reported in the early 1980s is a successful multi-component reaction for the synthesis of various 3-substituted indoles.[1] Up to now, this three-component reaction involving indole, aldehyde, and an active methylene compound has been the subject of numerous investigations, but most of these protocols usually employed Meldrum's acid as the reagents due to its high activity.[2] Only few examples extended the active methylene derivatives to malonesters,[3] barbituric acid,[4] dimedone,[5] and 4-hydroxycoumarin.[6] Malononitrile is a valuable nucleophile which can then be conveniently transformed into carboxylic acid, ester, amine, or amide groups.[7] However, it exhibits lower acidity and nucleophilicity compared with Meldrum's acid.[8] This sufficiently rationalizes why the Yonemitsu type reaction based on indole, benzaldehyde, and malononitrile need harsh conditions such as long reaction time and high catalyst loading. Until 2011, Zhou reported this reaction could be catalyzed by Cu(II)/Salen complex with 1.0 equiv. KH_2PO_4 as additive.[9] Arjan reported an extensive investigation using Zn(II)/Salen complex as mediators in the presence of 1.0 equiv. diisopropylethylamine as base.[10] After that, a ligand-free reaction was developed which utilizes $Cu(OAc)_2$ as catalyst and 1.0 equiv. KH_2PO_4 as additive.[11] Wan and co-workers found that 1.0 equiv. KH_2PO_4 in the mixture of H_2O and PEG-200 could promote this reaction.[12] More recently, tetrabutylammonium fluoride,[13] tetrabutylammonium glycinate ionic liquid,[14] *L*-proline,[15] glycine,[16] and $H_3PW_{12}O_{40}$[17] were employed to promote this condensation. Although some improvements have been achieved, searching for more general, efficient, and high yielding route to realize this significant transformation remains a valid exercise.[13-15]

Deep-eutectic solvents (DES) have drawn considerable attention in recent years due to their less toxicity, high biodegradability, comparatively low price, and straightforward synthesis.[18] These features made the applications of DES increasingly popular and DESs have been widely utilized as efficient reaction medium or catalyst in organic synthesis.[19] Our research group has interested in developing synthetic methodologies for useful organic compounds and a part of our efforts has been focused on improving Yonemitsu condensation.[20] Based on our empirical experience, herein, we screen an appropriate DES as catalyst with the hope of addressing this challenging reaction of indole, benzaldehyde and malononitrile (**Scheme 1**).



1 **2** **3** **4a-4r**

Scheme 1. Approach for the reaction of aldehyde, malononitrile and indole

As a starting point, benzaldehyde, malononitrile and indole were selected as model substrates to investigate the feasibility of our methodology (**Table 1**). Surprisingly, this three-component reaction cannot be efficiently achieved in anhydrous ethanol and afforded arylmethylenemalononitrile as the main product via Knoevenagel condensation between malodinitrile and aldehyde (**Table 1**, entry 1). Based on our empirical experience, adding water could assist the Yonemitsu reaction.[20] Thus, this strategy was tested. Product **4a** was furnished in a satisfactory result in the presence of water as we expected. After preparation of different DES, it was found that choline chloride and 1,3-dimethylurea (ChCl-DMU) has the highest catalytic efficiency (**Table 1**, entry 2). In order to confirm the effect of DES, this reaction was tested in aqueous ethanol without catalyst. The Knoevenagel condensation product was obtained too and almost no target product was probed (**Table 1**, entry 3). Solvents including ethyl lactate and methanol mixed with water were probed but the results were poor (**Table 1**, entries 6, 7). In order to further increase reaction yield, the solvent was finely tuned by employing ethanol with water in different volumes and proportions. After some experimentations, we were pleased to find that 0.8 mL ethanol and 0.2 mL water was the best choice in which this conversion took place with maximum isolated yield. We also observed that increasing the amount of indole to 0.55 mmol afford **4a** in 85% yield. To achieve the most suitable conditions, model reaction was tentatively run in different temperature, catalyst loading, and time. Optimization result indicated that reacted at 50 °C for 36 h and utilizing 10 mol% of ChCl-DMU were efficient to promote this reaction. Target molecule could form and isolate in 95% yield after washing with 50% ethanol. Therefore, this reaction was optimized using a cheap, safe, and environmentally benign medium and catalyst.

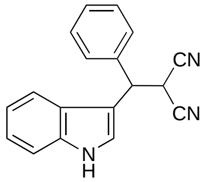
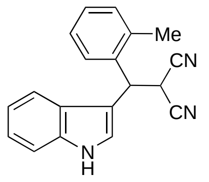
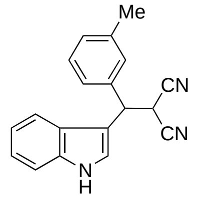
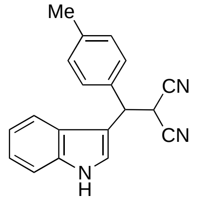
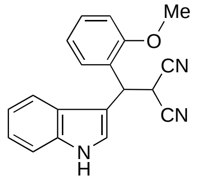
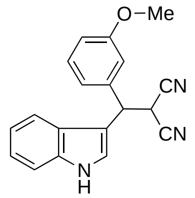
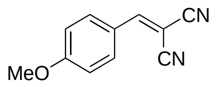
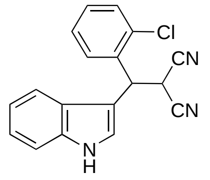
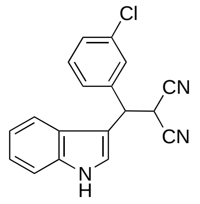
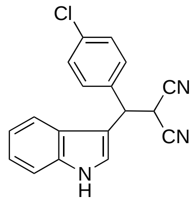
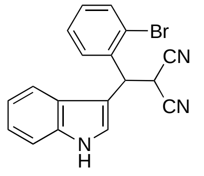
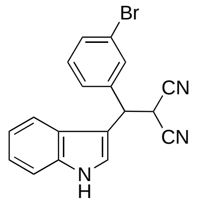
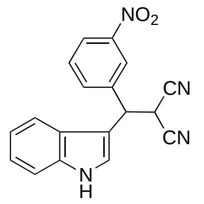
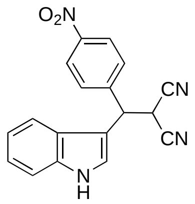
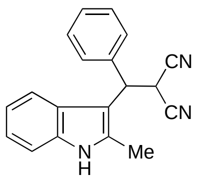
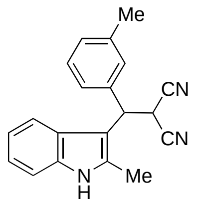
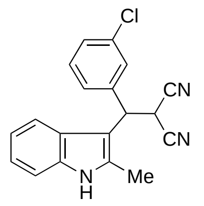
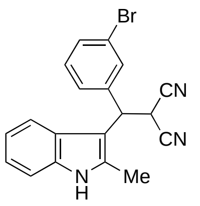
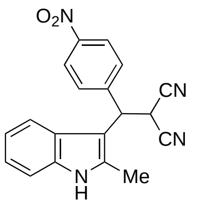
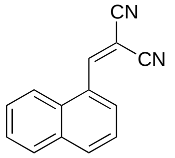
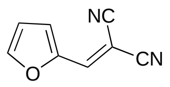
Table 1. Optimization of the reaction conditions for the synthesis of **4a**

Entry[a]	Catalyst/mol%	Solvent	Vol./mL	Temp./°C	Time/h	Yield[b]/%
1	ChCl-DMU 20%	EtOH	1.0	30	40	trace
2	ChCl-DMU 20%	EtOH-H_2O	0.6/0.4	30	40	73
3	--	EtOH-H_2O	0.6/0.4	30	40	trace
4	ChCl-urea 20%	EtOH-H_2O	0.6/0.4	30	40	68
5	ChCl-acetic acid 20%	EtOH-H_2O	0.6/0.4	30	40	24
6	ChCl-DMU 20%	MeOH-H_2O	0.6/0.4	30	40	45
7	ChCl-DMU 20%	ethyl lactate-H_2O	0.6/0.4	30	40	--
8	ChCl-DMU 20%	EtOH-H_2O	1.2/0.8	30	40	67
9	ChCl-DMU 20%	EtOH-H_2O	0.8/0.2	30	40	80
10	ChCl-DMU 20%	EtOH-H_2O	0.9/0.1	30	40	66
11[c]	ChCl-DMU 20%	EtOH-H_2O	0.8/0.2	30	40	85
12[c]	ChCl-DMU 20%	EtOH-H_2O	0.8/0.2	40	40	89
13[c]	ChCl-DMU 20%	EtOH-H_2O	0.8/0.2	50	40	94
14[c]	ChCl-DMU 20%	EtOH-H_2O	0.8/0.2	60	40	91
15[c]	ChCl-DMU 10%	EtOH-H_2O	0.8/0.2	50	40	95
16[c]	ChCl-DMU 5%	EtOH-H_2O	0.8/0.2	50	40	79
17[c]	ChCl-DMU 10%	EtOH-H_2O	0.8/0.2	50	36	95

[a] The reactions were carried out with benzaldehyde, malononitrile and indole in equimolecular amounts of 0.5 mmol. [b] Isolated yield. [c] Indole 0.55 mmol.

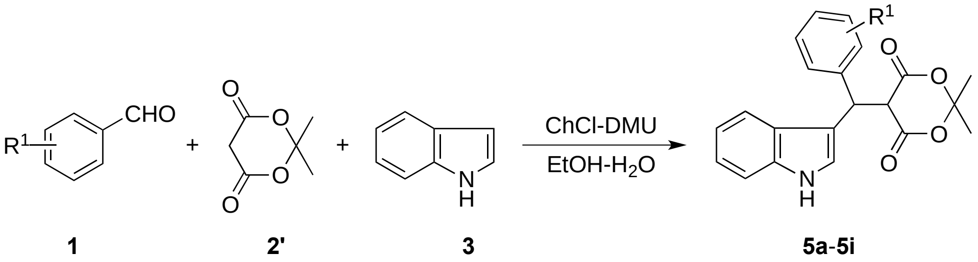
With the best experimental conditions in hand, we turned our attention to check the generality as well as the effectiveness of our protocol. Initially, a broad range of aromatic aldehydes were investigated under identical reaction conditions in **Table 2** to furnish the corresponding 3-substituted indoles (**4a**-**4r**) in good to excellent yields. Due to the disfavored influence of electronic and steric effects of some substituted aromatic aldehyde, we increased the catalyst load to 20 mol%. The results showed that the electronic effect played a major role in governing the reactivity of the substrates. Irrespective of presence of electron withdrawing groups in the ortho, meta or para positions on the ring of aromatic aldehydes, reactions proceeded smoothly to furnish desired products in high yields at 30 °C. Introduction of strongly electron-withdrawing group on benzene ring such as nitro not only favored to the yield of reaction, but also accelerated the reaction rate (**4l**, **4m**). Whereas, electron-rich substrates were transformed into the corresponding products in a relatively lower yield. With increasing the electron donating substituents on aromatic ring, activity was further decreased. So, methoxy substituted aromatic aldehydes gave worse results than methyl.

Table 2. Substrate scope for the synthesis of product **4**

 **4a** (50 °C, 95%)	 **4b** (50 °C, 82%)^c	 **4c** (50 °C, 97%)	 **4d** (50 °C, 76%)
 **4e** (50 °C, 76%)^c	 **4f** (50 °C, 94%)	 major product	 **4g** (30 °C, 97%)^c
 **4h** (30 °C, 97%)	 **4i** (30 °C, 97%)	 **4j** (30 °C, 95%)^c	 **4k** (30 °C, 97%)
 **4l** (30 °C, 92%)^{c,d}	 **4m** (30 °C, 97%)^d	 **4n** (30 °C, 97%)	 **4o** (30 °C, 97%)
 **4p** (30 °C, 98%)	 **4q** (30 °C, 98%)	 **4r** (30 °C, 98%)^d	 major product  major product

^{a} Reaction condition: aldehyde (0.5 mmol), malononitrile (0.5 mmol), indole (0.55 mmol), 20% mmol catalyst and 1 mL EtOH-H_2O (4:1) were stirred for 36 h. ^{b} Isolated yield. ^{c} Separated by column chromatography. ^{d} Reaction time: 12 h.

Unfortunately, 4-methoxybenzaldehyde and 4-bromobenzaldehyde even gave the Knoevenagel condensation adducts as main products. However, electron releasing group at the 3-position of aromatic aldehyde gave the desired products in good yields. Based on the mechanism, we think this outcome arose from the conjugation effect. The stronger positive p-π conjugated methoxyl substituent caused electron density of carbonyl carbon atom in benzaldehyde and exocyclic double bond in Knoevenagel condensation intermediate to enhance. But above result was harmful to both two steps of this reaction, especially when Michael addition of electron-rich indole with high electron density double bond of Knoevenagel adduct was performed. In contrast, presence of methoxy in meta-position on benzene ring had weak electron-withdrawing inductive effect and no conjugation effect. So, it afforded a better yield. Encouraged by these results, we replaced the substrate of indole with 2-methylindole and repeated the reaction at 30 °C (**Table 2**, **4n**-**4r**). Compared with the initial reaction, the corresponding products obtained in better yields. Unfortunately, when employing furfural or 1-naphthaldehyde as substrate, Knoevenagel adduct was the major product. Mainly due to they are also the electron rich aromatic aldehyde.



Scheme 2. Approach for the reaction of aldehyde, Meldrum's acid and indole

To highlight the applicability of our developed catalytic system, we further employing Meldrum's acid as reagent reacted with indole and various aromatic aldehydes (**Scheme 2**). Indeed, syntheses of corresponding 3-substituted indoles could achieve in excellent yields. The reaction time shorten to 7

Table 3. Substrate scope for the synthesis of product **5**

Entry[a]	R	Product	Yield[b]/%
1	C_6H_5	**5a**	94
2	3-MeC_6H_4	**5b**	95
3	4-MeC_6H_4	**5c**	81
4	3-$MeOC_6H_4$	**5d**	92
5	2-ClC_6H_4	**5e**	97
6	3-ClC_6H_4	**5f**	97
7	3-BrC_6H_4	**5g**	96
8	3-$NO_2C_6H_4$	**5h**	94
9	4-$NO_2C_6H_4$	**5i**	98

[a] Reaction condition: aldehyde (0.5 mmol), Meldrum's acid (0.55 mmol), indole (0.50 mmol), 20% mmol catalyst and 2 mL EtOH-H_2O (4:1) were stirred at 40 °C for 7 h. [b] Isolated yield.

hours and reaction temperature reduced to 40 °C with 20 mol% catalyst in 2 mL aqueous ethanol (**Table 3**). However, aliphatic aldehyde as the reactant had bad reactivity in this two reaction system.

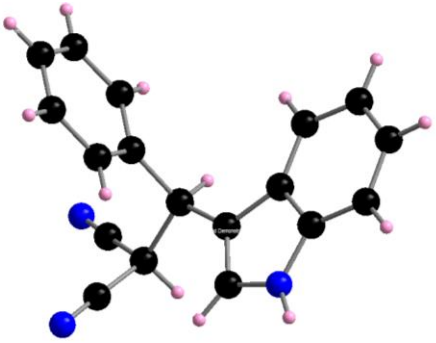


Figure 1. Crystal structure of compound **4a** (CCDC. 1543655)

With the hope of further investigating the mechanism, several control experiments were tested (**Figure 2**). We firstly verified the reaction of benzaldehyde and malononitrile with 10 mol% ChCl-DMU at 50 °C whether working well in the presence of water. 2-Benzylidenemalononitrile was obtained in 95% yield after about 10 min in 1 mL solvent (EtOH-H_2O 4:1, v/v) and only 64% yield was obtained without water (**Figure 2**, run 1). Based on the mechanism of this type reaction, Michael addition of indole and the above Knoevenagel adduct were performed with 10 mol% ChCl-DMU at 50 °C for 36 h. A larger gap was got and almost no target product generated in the absence of water (**Figure 2**, run 3). These results in accord

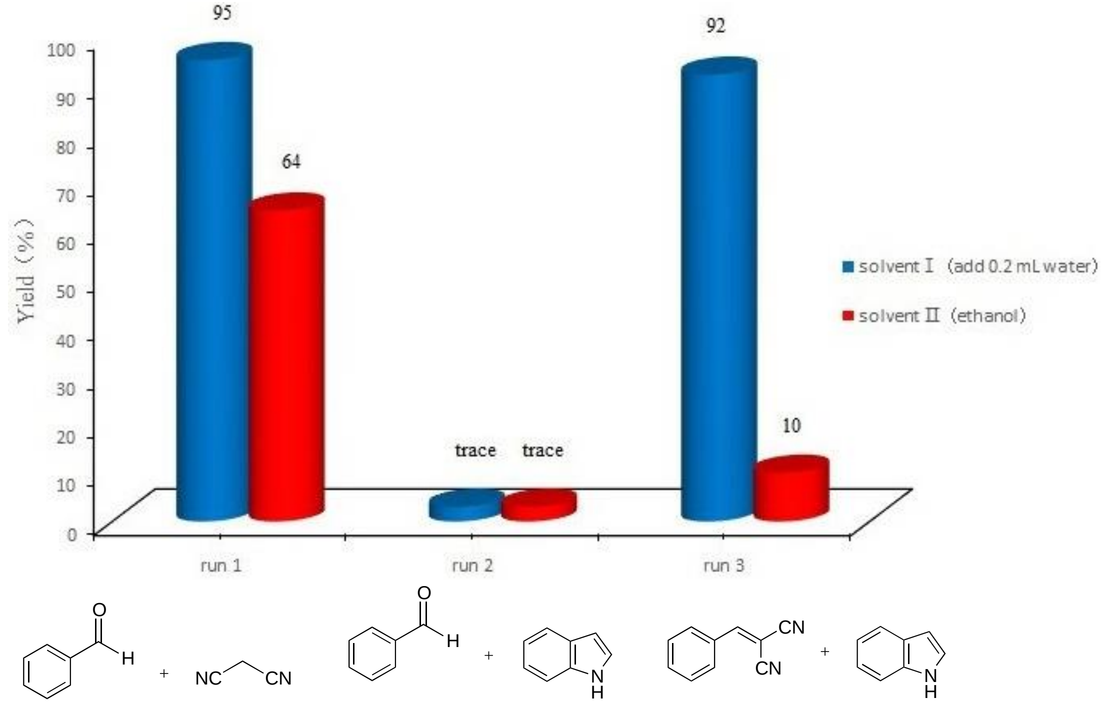
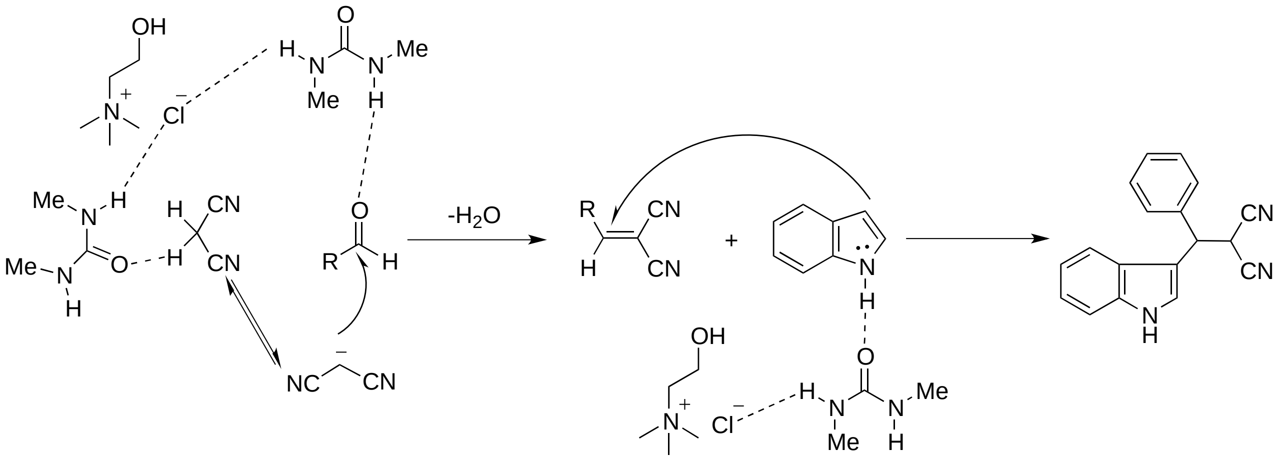


Figure 2. Control experiments (run 1, benzaldehyde and malononitrile; run 2, benzaldehyde and indole; run 3, 2-benzylidenemalononitrile and indole)

with our early experiences to conduct the Yonemitsu reaction and indicated that water could greatly accelerate the two step of Yonemitsu type reaction. Fortunately, when we treated benzaldehyde with indole in solvent I or solvent II, almost no 3-indolylmethanol and bis(indolyl)methane generated after reacted at 50 °C for 36 h (run 2). Avoiding this side reaction could safeguard to obtain the desired products with high yields.

According to the literature,[18d,18e] we propose the plausible mechanism of this reaction in **Scheme 3**. First, both the starting malononitrile and the aldehyde was activated by the DES through hydrogen binding. The Knoevenagel condensation was assisted and led to the formation of arylidenemalononitrile. Then the Knoevenagel adduct undergo the Michael addition with indole to give the final desired product. In this step, the nucleophilicity of indole could also be increased by DES through hydrogen bonding.



Scheme 3. Proposed mechanism of this reaction

In summary, we have provided a practical method to achieve the attractive Yonemitsu-type reaction of indoles, aldehydes and malononitrile. Firstly, utilizing readily available choline chloride-dimethylurea deep eutectic salts as catalyst and water as assistor is found to be valid. Furthermore, this method has broad substrates scope and affords target 3-substituted indoles in good to excellent yields. Last but not least, avoided the problems associated with using expensive and complicated catalyst.

EXPERIMENTAL

Martials and methods

Commercial solvents and reagents were used as received, except for benzaldehyde, which was used as a fresh distilled sample. High resolution mass spectra (HRMS) were obtained on an Agilent 6540 UHD Q-TOF mass spectrometer. Melting points were measured on Beijing Tech X-5 melting point detector and were uncorrected. FT-IR spectras were determined on Bruker Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C

NMR spectras were recorded on Bruker Avance 500 MHz or Bruker Avance III 400 MHz. X-Ray crystal spectra was obtained on Bruker Smart APEX II.

General procedure for the synthesis of 4a-4r

0.50 mmol Aldehyde, 0.50 mmol malononitrile, and 0.10 mmol catalyst were taken in 1 mL solvent (EtOH-H_2O 4:1, v/v). This solution was stirred in a 10 mL pressure tube at the stipulated temperature mentioned in Table 2 for 10 min, then 0.55 mmol indole was added and continuously reacted. After completion, 0.6 mL water and 0.4 mL EtOH was added and vigorously stirred for 10 min to remove the impurity and catalyst. This mixture was filtered and washed with 50% cold aqueous EtOH.

General procedure for the synthesis of 5a-5i

0.50 mmol Aldehyde, 0.55 mmol Meldrum's acid, and 0.10 mmol catalyst were taken in 2 mL solvent (EtOH-H_2O 4:1, v/v). This solution was stirred in a 10 mL pressure tube at 40 °C for 10 min, then 0.50 mmol indole was added and continuously reacted. After completion of the reaction, 1.0 mL 40% EtOH was added and vigorously stirred for 10 min to remove the impurity and catalyst. The mixture was filtered after cooling in ice bath. The precipitate was washed with 75% cold EtOH without further purification to afford the desired products.

ACKNOWLEDGEMENTS

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