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# DABCO-Amberlyst®15: A versatile heterogeneous catalyst in the multicomponent synthesis of tetrahydronaphthalenes and tetrahydroquinolines

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Union of MCRs
$MCR^2$
Green
DABCO supported on Amberlyst® 15
Recyclable
Cheap
Heterogeneous

A B S T R A C T

Bicyclic *ortho*-amino carbonitriles (tetrahydronaphthalenes) are crucial in their role to develop other heterocyclic compounds such as dicyanoanilines which can be used in optical electronic (optronic) devices. Tetrahydronaphthalenes can be obtained via the four-component reaction of malononitrile (2 equivalents), a cyclic ketone and an aldehyde. On the other hand, 5,6-substituted-2-amino-3-cyanopyridines (tetrahydroquinolines) have been found to be potent anti-cancer, anti-hypertensive, anti-microbial and anti-inflammatory agents. The synthesis of such compounds is directly linked by the single reactant replacement (SRR) technique because they derive from the combination of malononitrile, a cyclic ketone, an aldehyde and ammonium acetate as a nitrogen source. In this study, the activity of the heterogeneous metal-free catalyst DABCO supported on Amberlyst® 15 was explored in relation to the synthesis of both mentioned scaffolds. To the best of our knowledge, there are no instances in the literature where this has been achieved using the same catalyst, furthermore a novel successful DABCO-Amberlyst®15 catalysed one-pot sequential combination of multicomponent reactions ($MCR^2$) was also reported.

## 1. Introduction

Multicomponent reactions (MCRs) are an important tool in the hands of the synthetic chemist because they result in the formation of complex products in one-pot fashion while eliminating the need to separate and isolate intermediates [1–3]. In so doing, waste is minimized and the starting materials which are necessary are often cheap and readily available, whereas products obtained by MCRs may be impossible to form in an otherwise stepwise fashion due to the convergent nature of the mechanism.

Derivatives of bicyclic *ortho*-amino carbonitriles (structure A in Fig. 1) are considered as important synthetic assets because they can be employed in the synthesis of various other heterocyclic compounds. For instance, they can be converted to the respective dicyanoanilines which are renowned for their optical properties (structure B in Fig. 1) [4,5]. In fact, the latter have high fluorescence quantum yields which means that they may serve as efficient molecular electronic devices or be employed in artificial photosynthetic systems in which there is the conversion of sunlight into a chemical fuel [4].

Bicyclic ortho-amino carbonitriles are typically synthesized via the pseudo-4-component one-pot combination of malononitrile (two equivalents), an aldehyde and a ketone (Scheme 1) [5]. The mechanism of the reaction can be termed as convergent because there is the initial separate formation of the Knoevenagel products (IV and V) of the aldehyde (I) and the ketone (III) with malononitrile (II); which intermediates (IV and V) eventually react together via a [4 + 2] Diels-Alder reaction to form (VII) before proton transfer (base-catalysed) results in the end product (VIII) (Scheme 2) [5].

The majority of catalysts employed to drive this reaction are ionic-liquid (IL) or homogeneous in nature and include: a dicationic DABCO-based IL [5], an ester-derivative IL of DABCO [6], DABCO itself [7], triethylamine acetate [8], benzyltriethylammonium chloride (TEBAC) [8], morpholine [9] *etc.* Although ionic liquids are often described as easy to use, stable, non-toxic and non-volatile, in order to be able to recover and reuse them, solvent extraction is required. In view of this there have also been approaches involving the use of heterogeneous catalysts which can be retrieved efficiently by filtration.

Examples include: sodium calcium diphosphate [10], borax [11] and

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cobalt tetra-2,3-pyridiniumporphyrazinato with sulfonic acid moieties [12]. The latter have their own limitations as they involve lengthy processes of preparation or require toxic solvents and expensive starting materials.

In close connection to the just mentioned reaction is the 4-component synthesis of 5,6-substituted-2-amino-3-cyanopyridines (a set of 2-aminonicotinonitriles, a. k.a. tetrahydroquinolines) that can be attained by performing a single reactant replacement of one of the equivalents of malononitrile with ammonium acetate (Scheme 3) [13]. It can be immediately perceived that the latter products are significantly similar to the *ortho*-amino carbonitriles.

In fact, as will be shown in the Results section, the synthesis of the 2-amino-3-cyanopyridines may involve the concomitant formation of the respective *ortho*-amino carbonitriles as side products; hence the association of the two reactions. Meanwhile, 2-amino-3-cyanopyridines have been shown to be potent anti-cancer agents as exemplified by the compound in Fig. 2 which exhibits autophagy activity of gastric cancer cells when the latter are exposed to it for 12 h at a concentration of 10 μM [14]. Furthermore, other derivatives have been discovered to exhibit anti-inflammatory, anti-hypertensive and anti-microbial activity [15–17].

The mechanism of the synthesis of 2-amino-3-cyanopyridines (Scheme 4) is also convergent in nature and entails the combination of the Knoevenagel product (V) (formed by the reaction between the aldehyde (I) and malononitrile (II)) and the enamine (VI) (formed by the reaction between the ketone (III) and ammonium acetate (IV)). Subsequently, base-catalysed cyclization (to form (VIII)) and enamine-imine tautomerization (leading to (IX)) take place. Ultimately, atmospheric oxygen causes the conversion of the dihydropyridine (IX) to the final pyridine product (X) [13].

Amongst the catalysts employed in the synthesis of 2-amino-3-cyanopyridines there are Amberlyst® 15 in acetonitrile solvent [13], ytterbium perfluorooctanoate (an expensive homogeneous ionic salt) [18], 2,2,2-trifluoroethanol (a toxic, carcinogenic solvent) [19], magnetite [20], copper iodide supported on activated charcoal nanoparticles (in acetonitrile solvent) [21], amino propylated-salicylaldehyde-copper (II)-zirconia-coated magnetite (a catalyst which requires a length procedure of preparation) [22], Vitamin B3 supported on magnetite [23], and magnetite-graphite carbon-nitride sulfonic acid composite [24].

In view of all the above, to the best of our knowledge, there has never been a study in which the synthesis of the two similar products was conducted in the presence of the same catalyst. Following a recent approach whereby the same metal-free and cheap catalyst was employed in diverse multicomponent reactions [25], previously reported DABCO@Amberlyst® 15 [26] was synthesized using a modified procedure and utilised in both syntheses to collect the pure products in appreciable yields. The below study serves as a further example to highlight how heterocycle formation can occur under basic conditions, as reported in other diverse instances in the literature [27,28].

## 2. Experimental

### 2.1. General reaction procedures

#### 2.1.1. Synthesis of bicyclic ortho-amino carbonitriles (tetrahydronaphthalenes) – products (4)

*2.1.1.1. Using catalyst DABCO-A15-A.* To a nitrogen-flushed dry 25-mL-two-necked flask, malononitrile (5.0 mmol), the aldehyde (2.5 mmol) and cyclohexanone (2.5 mmol) were added in that order followed by 7:3 ethanol/water (4 mL) and the catalyst (0.089 g, 10 mol%, 2.8 mmol/g loading). The mixture was left to stir for approximately 10 min at room temperature before heating to the required temperature (80 °C). The reaction was monitored via TLC at 1-h intervals and was stopped until complete consumption of the malononitrile (visible after leaving TLC plate in an iodine-saturated chamber). Subsequently, the reaction mixture was dissolved in hot acetone, filtered and then concentrated under vacuum by rotary evaporation set at 45 °C/-1 bar. The crude solid was then recrystallized from ethanol.

*2.1.1.2. Using catalyst DABCO-A15-B.* To a nitrogen-flushed dry 25-mL-two-necked flask, malononitrile (5.0 mmol), the aldehyde (2.5 mmol) and cyclohexanone (2.5 mmol) were added in that order followed by dry ethanol (4 mL)) and the catalyst (0.24 g, 20 mol%, 2.1 mmol/g loading). The mixture was left to stir for approximately 10 min at room temperature before heating to the required temperature (95 °C). The reaction was monitored via TLC at 1-h intervals and was stopped until complete consumption of the malononitrile (visible after leaving TLC plate in an iodine-saturated chamber). Subsequently, the reaction mixture was dissolved in hot acetone, filtered and then concentrated under vacuum by rotary evaporation set at 45 °C/-1 bar. The crude solid was then recrystallized from ethanol.

#### 2.1.2. Synthesis of 5,6-substituted-2-amino-3-cyanopyridines (tetrahydroquinolines) – products (6)

To a nitrogen-flushed dry 25-mL-two-necked flask, malononitrile (2.5 mmol) and the aldehyde (2.5 mmol) were added in that order followed by methanol (4 mL)) and the catalyst (0.12 g, 10 mol%, DABCO-A15-B). The mixture was left to stir for approximately 1 h at 70 °C before adding ammonium acetate (3.75 mmol) and cyclohexanone (2.5 mmol) and leaving to stir further. The reaction was monitored using TLC at 1-h intervals and was stopped until complete consumption of the

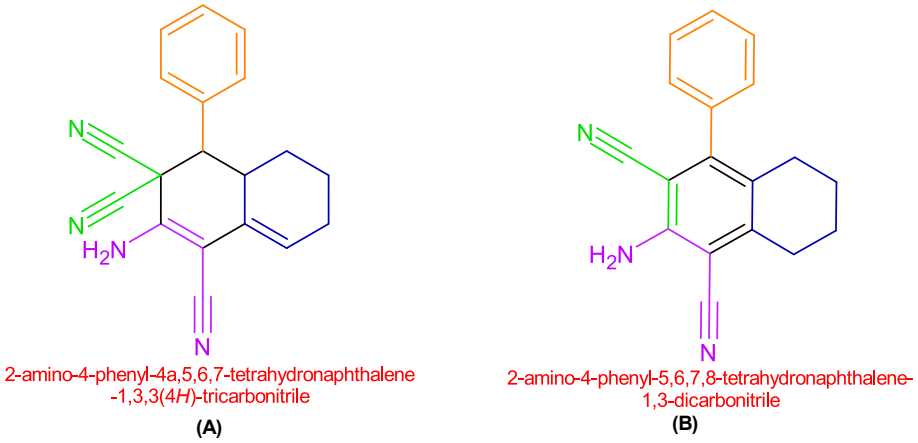



**Fig. 1.** Bicyclic ortho-amino carbonitrile (A) and bicyclic 2,6-dicyanoaniline (B).

intermediate (top end of the TLC plate) and until the spot belonging to the reduced product (lowest spot on TLC, using 7:3 hexane/ethyl acetate as solvent mixture) was very weak or did not change in intensity. Subsequently, the reaction mixture was dissolved in hot ethanol, filtered and then concentrated under vacuum by rotary evaporation set at 40 °C/-1 bar. The crude solid was then recrystallized from ethanol.

#### 2.1.3. Synthesis of MCR$^2$ products – products (8)

To a nitrogen-flushed dry 25-mL-two-necked flask, malononitrile (2.5 mmol), terephthaldehyde (2.5 mmol) and 1-naphthol/2-naphthol (2.5 mmol) were added in that order followed by dry ethanol (4 mL) and the catalyst (0.36 g, 30 mol%, 2.1 mmol/g loading). The mixture was left to stir for approximately 10 min at room temperature before heating to the required temperature (80 °C). The reaction was monitored via TLC at 1-h intervals and was stopped (after 5 h) until complete consumption of the 1-naphthol/2-naphthol or upon no further change in spot intensity. Subsequently, malononitrile (5.0 mmol) and *c*-hexanone (2.5 mmol) were added to the same reaction flask and reaction left to stir further until complete consumption of the chromene intermediate. Finally, the reaction mixture was dissolved in hot acetone, filtered and then concentrated under vacuum by rotary evaporation set at 40 °C/-1 bar. The crude solid was then redissolved in a minimal amount of acetone before loading onto a silica gel column and eluted with 6:4 → 5:5 hexane/ethyl acetate.

### 2.2. Catalyst synthesis

#### 2.2.1. Piperazine/DABCO supported on Amberlyst® 15 (Pip/DABCO-A15)

To a nitrogen-flushed dry 50-mL single-necked flask, 0.6 g of Amberlyst 15®, previously dried at 120 °C in an air-oven for 12 h, was added followed by 1–2 mL of ethanol solvent. Subsequently, 0.4 g of the amine (piperazine, DABCO) were added to the flask. The mixture was left to stir for 36 h at RT after which it was filtered through a G4 Hirsch funnel. The solid catalyst was heated further for 12 h at 80 °C in an air oven before leaving in a desiccator for 12 further hours and then taking note of the mass difference compared to that of Amberlyst 15®. Finally, the catalyst was transferred to a pestle and mortar and ground into a fine powder. This is denoted as DABCO-A15-A.

Contrastingly, in the synthesis of DABCO-A15-B, after filtration, the solid catalyst was heated under vacuum at 120 °C for 8 h in a round-bottomed flask in an oil bath before grinding into a fine powder.

#### 2.2.2. Piperazine/DABCO/DBU supported on chloropropylsilylated silica (Pip-$SiO_2$, DABCO-$SiO_2$. DBU-$SiO_2$)

The method employed is a slightly modified version of that suggested by Hasaninejad, A. et al. [29]. Silica (25 g) was first immersed in 6 M hydrochloric acid for 24 h and then washed repeatedly with water before drying under vacuum and then in an oven at 120 °C for 24 h. The final product is termed as activated silica.

A mixture of dry toluene (30 mL) and activated silica (2.5 g) was refluxed for 48 h after addition of 3-chloropropyltrimethoxysilane (2.5 mL) and triethylamine (0.25 mL) [30]. The chloropropylsilylated silica was then filtered, washed with toluene (30 mL) and with acetone (30 mL) before leaving to dry in desiccator for 24 h. The final product is termed as chloropropylsilylated silica.

Subsequently, DABCO, piperazine or DBU (5 mmol) were added to the chloropropylsilylated silica (1.0 g) in 30 mL of dry acetone and the latter mixture was refluxed for 36 further hours before filtering, washing with further acetone and then leaving to dry in desiccator [31]. For the preparation of DBU-$SiO_2$ the solvent used was cyclohexane instead of acetone.

MgO was prepared according to Ref. [32] and Cell-$NH_2$ was prepared as per method [33].

#### 2.2.3. Determination of alkalinity of catalysts

The prepared catalyst was ground into a fine powder and then stirred (0.05 g) in 10 mL aqueous hydrochloric acid (0.02 M) for 2 h at room temperature in a 50-mL round-bottomed single-neck flask fitted with a cap. Subsequently, catalyst was filtered, washed with deionised water (3 × 10 mL) before titrating the filtrate with aqueous sodium hydroxide (0.02 M) using 10 % w/v alcoholic phenolphthalein solution as an indicator to a slightly-pink end-point.

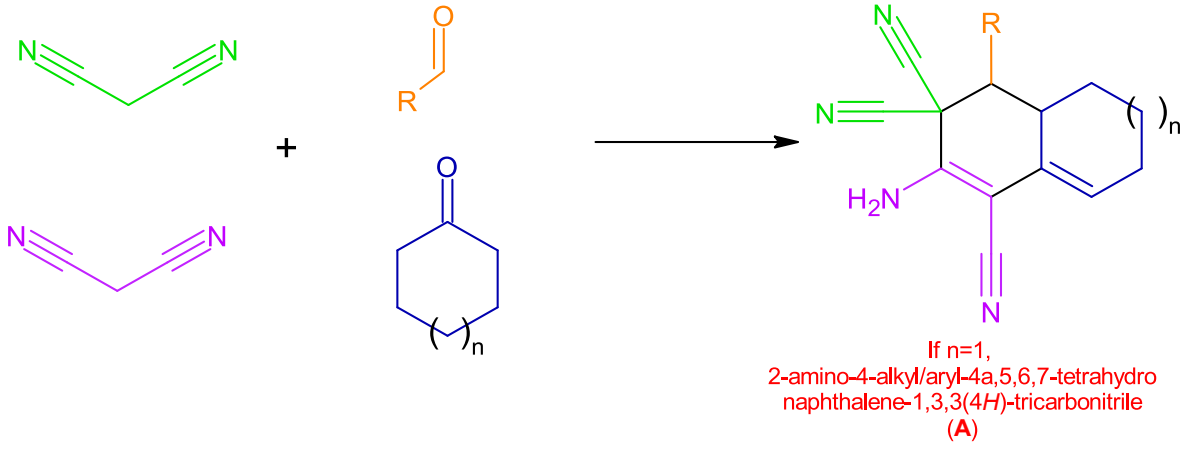
Contrastingly, A15 was back titrated the other way round in order to determine its acidic content i.e. it (0.05 g) was stirred with aqueous sodium hydroxide (10 mL, 0.02 M) for 2 h, filtered, washed with deionised water (3 × 10 mL) and then the filtrate was titrated with aqueous hydrochloric acid (0.02 M) using the same indicator to a colourless end point.

## 3. Results and discussion

### 3.1. Catalyst synthesis variations

As will be elaborated further below, the catalyst of choice was DABCO supported on crushed and pulverised Amberlyst® 15 beads (DABCO-A15). However, following initial recycling runs, the original method of catalyst preparation (resulting in catalyst labelled as DABCO-A15-A) had to be tweaked to minimise leaching during the reaction and to make it more recyclable. The latter modifications yielded the catalyst labelled as DABCO-A15-B which was deemed to be the most ideal (Table 1, entry 19).

The first method of catalyst preparation entailed stirring DABCO (0.4 g) and Amberlyst® 15 beads (0.6 g) in ethanol solvent (1 mL) at RT

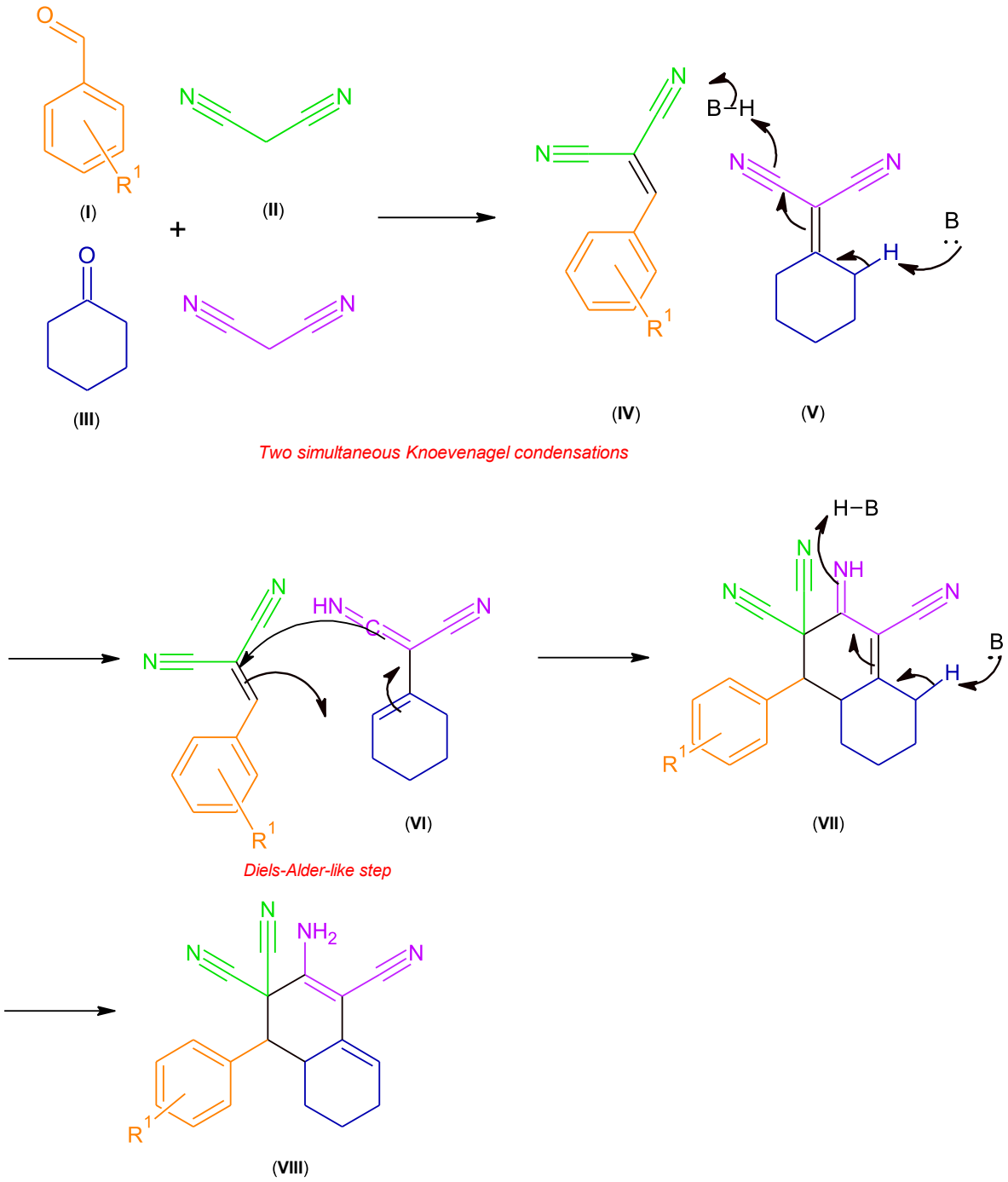



**Scheme 1.** One-pot synthesis of bicyclic ortho-amino carbonitriles (tetrahydronaphthalenes) from malononitrile (two equivalents), an aldehyde and a ketone [5].

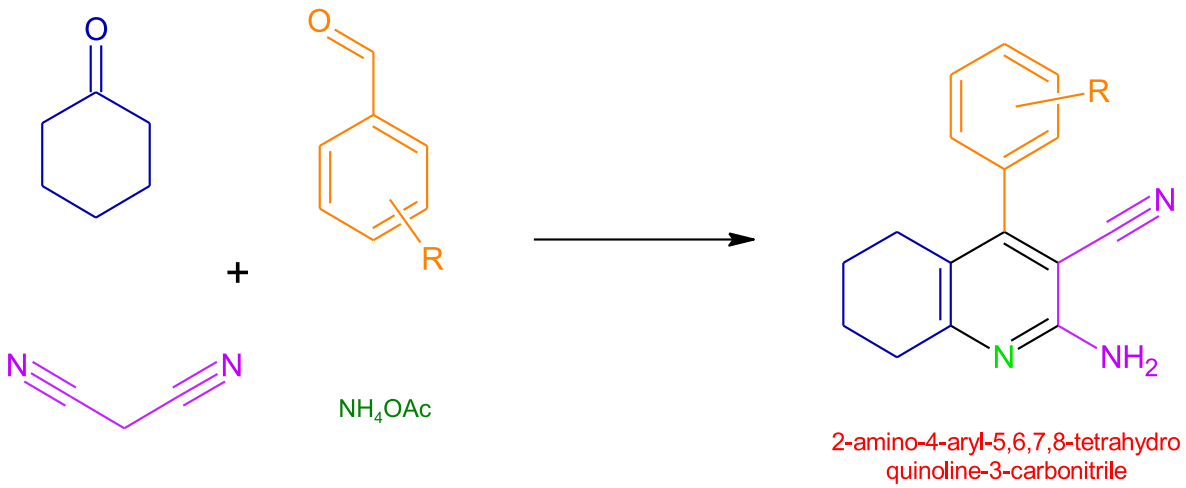
for 48 h before filtering, washing copiously with ethanol and leaving to dry in an air oven at 80 °C for a few hours and then in desiccator overnight. Ultimately the catalyst was crushed and pulverised with a pestle and mortar. The loading of DABCO on A15 was found to be 2.8 mmol/g (by mass) and the catalyst was denoted as DABCO-A15-A.

In the second method, the same procedure was followed. However, after the final filtration, the catalyst was left to dry at 100–120 °C under vacuum for 12 h. The latter was performed so as to sublime off the chemically-unbonded DABCO which was trapped within the polymeric matrix. In fact, the loading decreased to 2.1 mmol/g (by mass) and this catalyst was denoted as DABCO-A15-B. In truth this decrease may be partially due to some trapped water within the polymer beads that evaporated off and resulted in a lower final loaded catalyst mass. However, since the A15 beads had been previously subjected to drying, the amount of weight loss due to water should have been minimal.

The postulated structures of the catalyst DABCO-A15 are those in Fig. 3 based on titrimetric analysis which was performed to determine the basicity of the catalyst. In short, firstly, the acid content of Amberlyst® 15 (previously dried at 120 °C for 12 h in a muffle furnace) was calculated by back titration with hydrochloric acid and found to be equal to 3.0 mmol/g. Then, DABCO-A15-B was also back titrated and the basic content was found to be equal to 1.0 mmol/g. Since the loading of DABCO-A15 was calculated to be 2.1 mmol/g (by mass difference), it follows that 1.0 mmol/g was in the form of A (Fig. 3) while the




**Scheme 2.** Mechanism of formation of bicyclic ortho-amino carbonitriles via a pseudo-4-component reaction of an aldehyde, a ketone and two equivalents of malononitrile (adapted from Ref. [5]).




**Scheme 3.** 4-Component synthesis of 5,6-substituted-2-amino-3-cyanopyridines (tetrahydroquinolines) from cyclohexanone, an aldehyde, malononitrile and ammonium acetate [13].

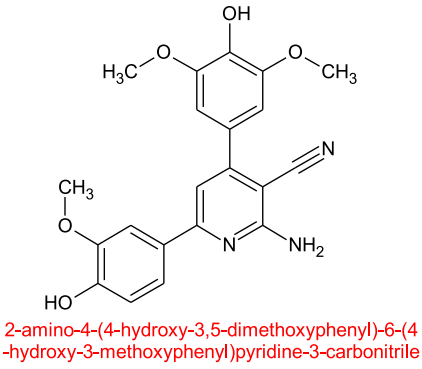



**Fig. 2.** 2-Amino-3-cyanopyridine which exhibited autophagy activity against gastric cancer cells [14].

remaining 1.1 mmol/g of DABCO was in the form of B. Such values agree with the previously denoted acidity value of Amberlyst® 15 since if 1.1 mmol/g of DABCO was bonded to 2 equivalent sulfonic acid moieties while 1.0 mmol/g was bonded to 1 equivalent sulfonic acid groups, then the total number of sulfonic acid groups in the catalyst according to these values is 1 + 2.2 = 3.2 mmol/g; which value is fairly similar to the value of 3.0 mmol/g (of free Amberlyst® 15).

In a separate procedure, the catalyst DABCO-A15-B was stirred with aqueous sodium hydroxide for 2 h, filtered and then the clear filtrate was back titrated with hydrochloric acid in order to determine the acidity of such catalyst. The final value was that of 1.3 mmol/g. This value can be justified by the following reasoning. When the catalyst is treated with sodium hydroxide it reacts both with free sulfonic acid groups (if any) and with the protonated DABCO to release free DABCO in solution. Hence, after filtration, both excess sodium hydroxide and free DABCO end up in the filtrate. It must be noted that during titration with HCl only one end of the DABCO molecules gets protonated up to the end point established by phenolphthalein indicator. For a gram of catalyst, if the initial amount of sodium hydroxide used is denoted as $x$, the sodium hydroxide which gets consumed is 1.0 mmol (for structure A which has one protonated nitrogen atom only, see Fig. 3) and $1.1 \times 2\ mmol = 2.2$ mmol for catalyst moieties having structure B. The amount of sodium hydroxide left in the filtrate is $x - (2.2 + 1.0) = x - 3.2$ mmol. However, in the filtrate there is now also 2.1 mmol of free DABCO (according to the mass loading). This means that during the titration with HCl, the latter reacts with $(x - 3.2) + 2.1 = x - 1.1$ mmol of total base. Considering that this is a back titration, in order to calculate the acidity, this amount of base is subtracted from the original amount of sodium hydroxide ($x$) resulting in a theoretical acidity value of $x-(x- 1.1)/1 = 1.1$ mmol/g which is fairly similar to the acidity value obtained.

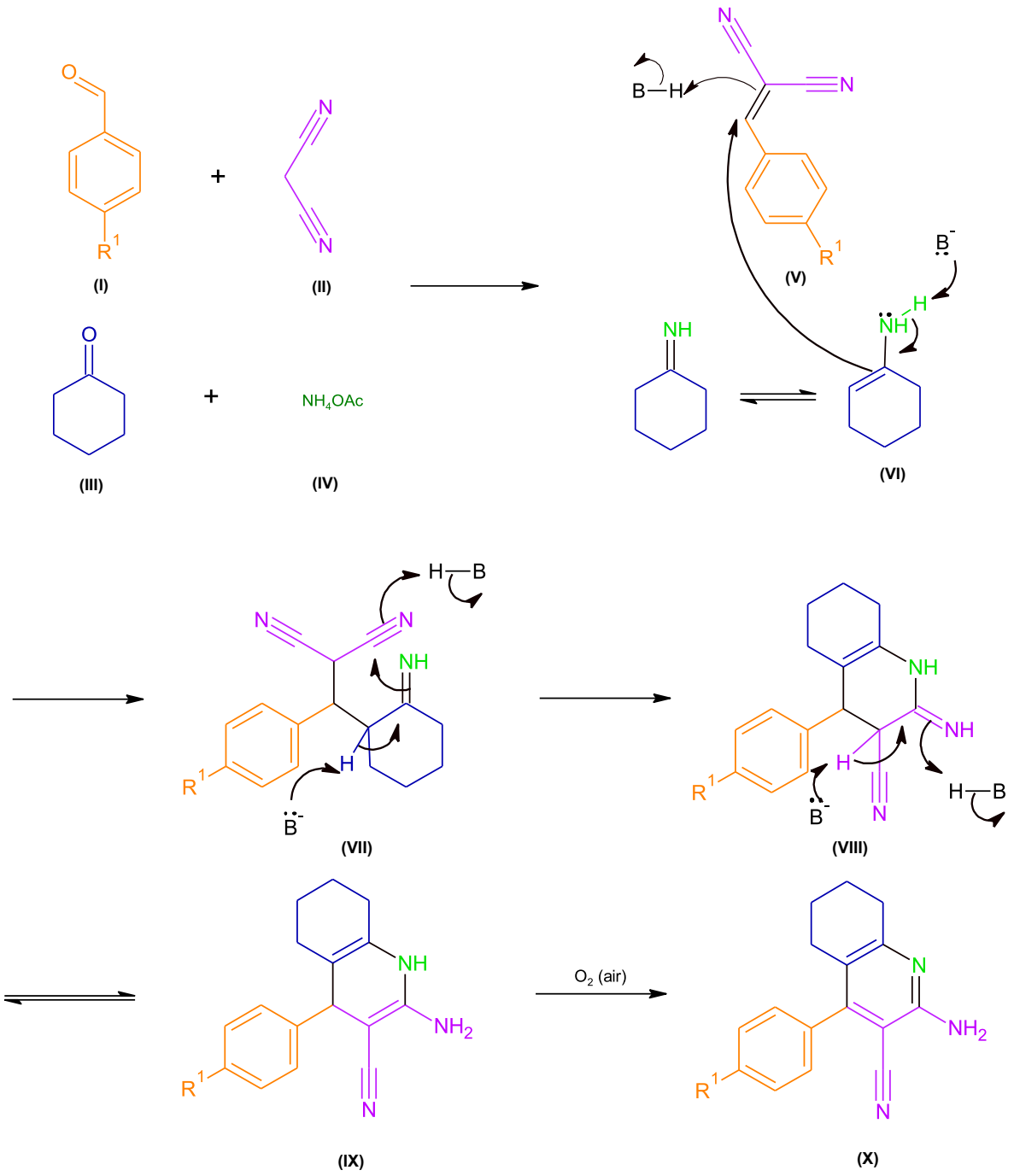
It is important to note that in a series of catalyst preparation batches it was observed that the DABCO loading in the final dry catalyst increased proportionally with the initial amount of DABCO stirred with Amberlyst® 15. However, when the amount of DABCO in the initial mixture was increased beyond 40 % w/w there was no change in the final loading which presumably means that Amberlyst® 15 had become saturated and all sulfonic acid groups (or nearly all of them) where interacting with a DABCO-N terminal.

In addition, even if theoretically not all sulfonic acid groups had reacted, the latter would have not affected the final titre value.

### 3.2. *Optimization runs for the synthesis of bicyclic ortho-amino carbonitriles (tetrahydronaphthalenes)*

In a set of catalyst screening and optimization runs, it was evident that even if the reaction could not proceed without a catalyst (entry 1, Table 1), the use of very strongly basic heterogeneous catalysts was detrimental to attaining high yields of bicylic *ortho*-amino carbonitriles. Both MgO (entries 2, 3, Table 1) and DBU-$SiO_2$ (entry 4, Table 1) performed below par compared to other less basic catalysts such as DABCO-$SiO_2$ and amino propylated cellulose (Cell-$NH_2$) (entries 5–7, Table 1). The latter was used at only 5 mol% owing to the low amino degree of functionalization (0.9 mmol/g). Positively when both DABCO-A15 (2.8 mmol/g) and Pip-A15 (2.72 mmol/g) were trialled separately (entries 8–25) better results were achieved with the former catalyst having a slight edge over the other. A possible reason for this can be once again attributed to the relative basicity of the two, DABCO being slightly less basic than piperazine ($pK_b$ in water of Piperazine = 4.2, DABCO = 5.3). DABCO-A15 (2.8 mmol/g) catalytic activity increased on moving from 5 mol% to 10 mol% but then decreased again on doubling the amount to 20 mol% (Table 1, entries 8, 9, 13). Furthermore, it was vividly apparent that the solvent played a crucial role. In fact, on changing from 7 : 3 ethanol/water to anhydrous ethanol, the yield decreased to 76 % (Table 1, entry 10).

Interestingly, when the reaction was performed using a reactant ratio of 1 : 1: 1 under the ideal conditions (85 °C, 7–3 ethanol/water, 10 mol% catalyst, entry 12), the same product (4a) was ultimately collected after recrystallization. GC analysis of the crude reaction mixture after 4 h showed that the product (4a), cyclohexanone (3a) and the aldehyde (2a) were in equal proportions confirming that the reaction was following the same mechanism irrespective of the fact that malononitrile was present at half the stoichiometric amount. Thence, half the stoichiometric




**Scheme 4.** Mechanism of formation of 2-amino-3-cyanopyridines from an aldehyde, a ketone, ammonium acetate and malononitrile (adapted from Ref. [13]).

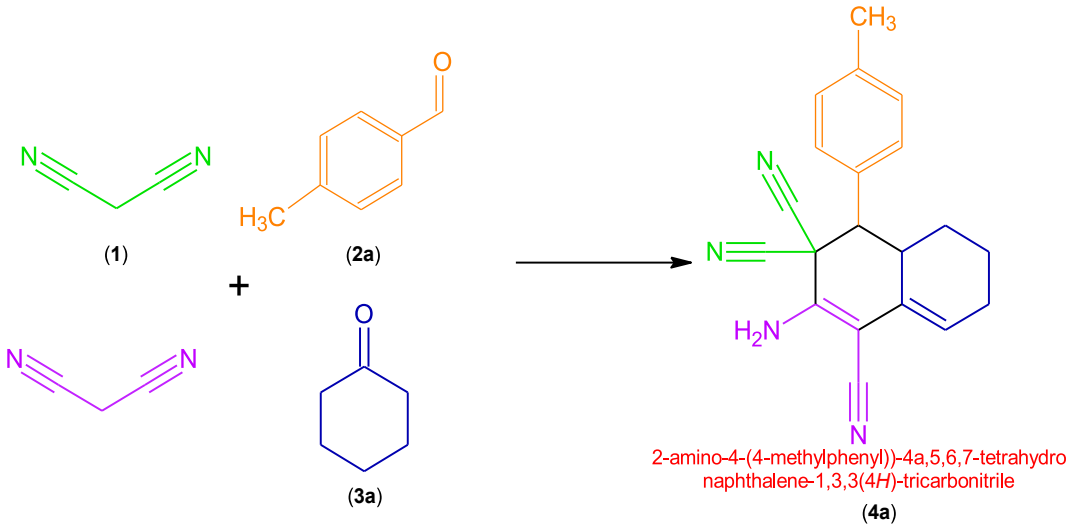
amount of product should have formed which indeed happened (yield = 48 %). Contrastingly, on repeating the trial at room temperature (entry 13) the reaction stopped at the Knoevenagel intermediate stage. The use of a slight excess of malononitrile did not contribute to a better result either (entry 14).

Performing the reaction on a 5.0 mmol scale (gram scale, theoretical yield of 1.57 g) yielded a nearly identical return of 88 % hence showing that the reaction can be upscaled unproblematically.

When the catalyst DABCO-A15-A (2.8 mmol/g) was reused in subsequent runs for the synthesis of the model reaction bicyclic *ortho*-amino carbonitrile 4a, it could be established that the catalyst remained moderately active for 5 consecutive runs.

At this point it was postulated that the reason behind the decrease in the yield between one recycling run and another (Fig. 4) could have been two-fold. Firstly, since the loading after heating the catalyst under vacuum was lower than that when it was simply dried in an oven and then in a desiccator, it probably meant that the original catalyst (DABCO-A15-A) had "free" DABCO trapped within the polymeric matrix that could leach slowly out in the reaction mixture. Secondly, the presence of water in the solvent mixture was potentially assisting this process to occur faster by "hydrolysing" the DABCO-A15 ionic interactions. In fact, when the DABCO-A15-A catalyst with a loading of 2.8 mmol/g was tried in ethanol as a solvent (Table 1, entry 10), the yield was lower than that in entry 9 where a mixture of ethanol/water was used. The yield drop was even sharper (entry 16) when DABCO-A15-B was used. In spite of this, it was discovered that the catalytic performance of DABCO-A15-B could be greatly improved by increasing the temperature, the reaction time and the catalytic molar loading to

**Table 1**
Optimization and catalyst screening runs for the synthesis of tetrahydronaphthalenes (4a) from two equivalents of malononitrile (1), *p*-tolualdehyde (2a) and cyclohexanone (3a).




| Entry[a] | Catalyst (loading of active component) | Amount of catalyst | Solvent | Temperature [°C]/Time (hrs) | Yield of 4a (%)[b] |
|---|---|---|---|---|---|
| 1 | No catalyst | – | EtOH – $H_2O$ (7 : 3) | 85/5 | – |
| 2 | MgO | 10 mol% | EtOH – $H_2O$ (7 : 3) | 85/5 | 68 |
| 3 | | 20 mol% | EtOH – $H_2O$ (7 : 3) | 85/5 | 67 |
| 4 | DBU-$SiO_2$ (0.6 mmol/g) | 10 mol% | EtOH – $H_2O$ (7 : 3) | 80/5 | 70 |
| 5 | DABCO-$SiO_2$ (0.9 mmol/g) | 10 mol% | EtOH – $H_2O$ (7 : 3) | 85/5 | 53 |
| 6 | | 20 mol% | EtOH – $H_2O$ (7 : 3) | 80/5 | 77 |
| 7 | Cell-$NH_2$ (0.9 mmol/g) | 5 mol% | EtOH – $H_2O$ (7 : 3) | 85/5 | 76 |
| 8 | DABCO-A15-A (powder) | 5 mol% | EtOH – $H_2O$ (7 : 3) | 85/5 | 80 |
| 9 | (2.8 mmol/g) | 10 mol% | EtOH – $H_2O$ (7 : 3) | 85/5 | 89 |
| 10 | | 10 mol% | EtOH | 85/5 | 76 |
| 11 | | 20 mol% | EtOH – $H_2O$ (7 : 3) | 85/4 | 82 |
| 12 | | 10 mol% | EtOH – $H_2O$ (7 : 3) | 85/4 | 48[c] |
| 13 | | 10 mol% | EtOH – $H_2O$ (7 : 3) | RT/2 | -[c,d] |
| 14 | | 10 mol% | EtOH – $H_2O$ (7 : 3) | 85/5 | 80[e] |
| 15 | | 10 mol% | EtOH – $H_2O$ (7 : 3) | 95/5 | 85 |
| 16 | DABCO-A15-B (powder) | 10 mol% | EtOH | 85/5 | 40 |
| 17 | (2.1 mmol/g) | 10 mol% | EtOH | 95/5 | 70 |
| 18 | | 15 mol% | EtOH | 95/5 | 80 |
| 19 | | 20 mol% | EtOH | 95/5 | 87 |
| 20 | | 20 mol% | EtOH – $H_2O$ (7 : 3) | 95/5 | 86 |
| 21 | DABCO-A15-B (beads) | 10 mol% | EtOH | 85/6 | 13 |
| 22 | (2.1 mmol/g) | 10 mol% | EtOH | 90/8 | 41 |
| 23 | | 10 mol% | EtOH – $H_2O$ (7 : 3) | 85/5 | 80 |
| 24 | Pip-A15 (powder) | 10 mol% | EtOH – $H_2O$ (7 : 3) | 85/5 | 85 |
| 25 | (2.72 mmol/g) | 20 mol% | EtOH – $H_2O$ (7 : 3) | 80/5 | 77 |

[a] Reaction performed on a 2.5 mmol scale in 4 mL of solvent mixture using a reactant molar ratio of 2 (malononitrile): 1 (aldehyde): 1 (ketone).
[b] Yield of pure product purified by recrystallization from ethanol and confirmed by IR, $^1$H NMR,$^{13}$C NMR, MS.
[c] Molar ratio used was 1 : 1: 1.
[d] Knoevenagel intermediate only formed.
[e] Molar ratio of 1: 2a: 3a was 2.2 : 1: 1; __ = best condition in terms of recyclability and product yield.

result in a practically identical final product yield (Table 1, entry 19, 87 %). Furthermore, when DABCO-A15-B was used in ethanol-water the yield remained the same (entry 20, 86 %) Positively, at these established conditions (of entry 19), DABCO-A15-B gave more consistent yields across 5 recycling cycles (Fig. 5) confirming that leaching was minimal and that catalysis was in all probability occurring in a heterogeneous manner rendering it the ideal catalyst in terms of green chemistry [34]. The same cannot be said for DABCO-A15-A which could have both homogeneous and heterogeneous aspects to it. In relation to this, DABCO as a homogeneous base was not trialled because it has been actually used by Pore, D. M. et al. [4]. Yet, in the latter study no recoverability was possible, a larger amount of solvent was used (5 mL per mmol as

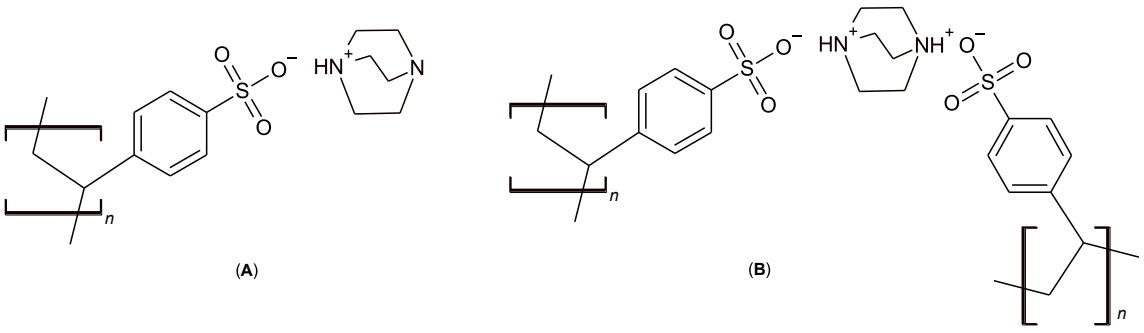



**Fig. 3.** Postulated structures of DABCO-A15-B.

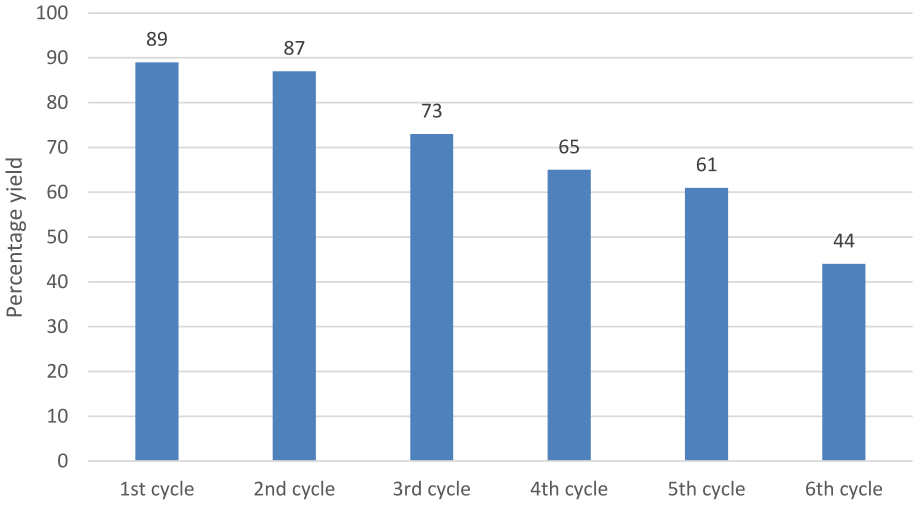



**Fig. 4.** Recycling runs for the synthesis of the model bicyclic ortho-amino carbonitrile (4a) using DABCO-A15-A.

opposed to 4 mL per 2.5 mmol in our study) and essentially, the yields were fairly similar (89 %) to ours albeit after 1 h only.

### *3.3. Optimization runs for the synthesis of 5,6-substituted-2-amino-3-cyanopyridines (tetrahydroquinolines)*

From the initial ventures into the reaction, it was discovered that the synthesis of 5,6-substituted-2-amino-3-cyanopyridines was in a close relation to that of tetrahydronaphthalenes because 4a was always produced as a side product along with the expected product 6a. Considering that DABCO-A15-B and Pip-A15 had both given good results in the synthesis of 4, both were tried under various conditions in order to form 6a. In addition, since in the literature Amberlyst® 15 had been used as a catalyst for the same reaction in acetonitrile solvent [13], it was postulated that its modification with DABCO or piperazine would possibly improve the yield while also allowing the execution of the reaction in a greener solvent.

A vital aspect pertaining to this reaction was that in order to form the

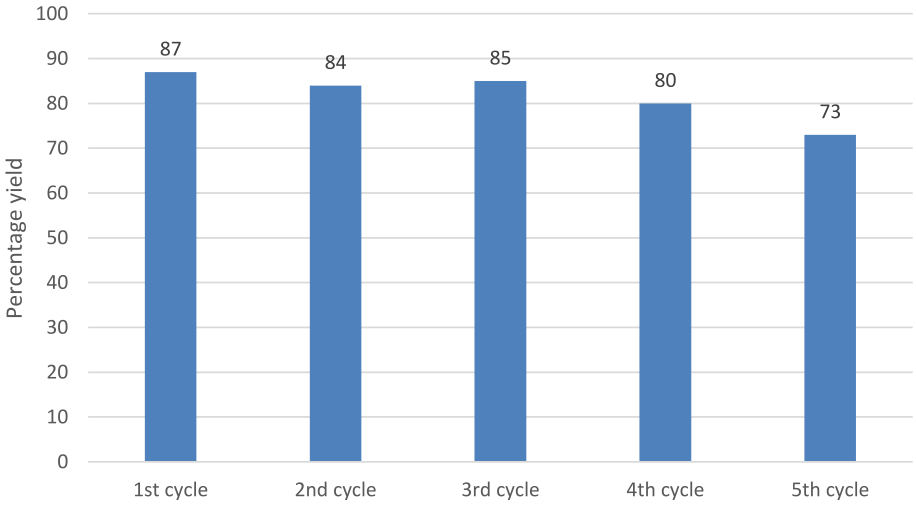



**Fig. 5.** Recycling runs for the synthesis of 4a using DABCO-A15-B.

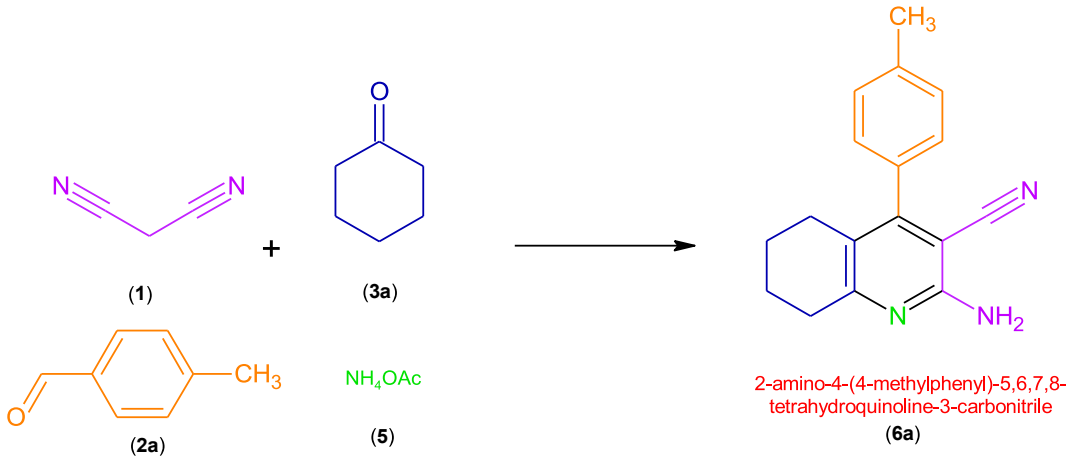
product, the aldehyde and malononitrile had to be first mixed together along with the catalyst and solvent to result in the Knoevenagel product before adding the ketone and ammonium acetate. When all reactants were mixed at the same time, little to no product was observed to be forming. Rather, product 4a got formed. A further crucial aspect to collect product 6a in pure form was by doing the work up using ethanol only (5–10 mL) and not using acetone (5–10 mL) because 4a tends to require more ethanol (approx. 50 mL) in order for it to dissolve. In this way, any formed 4a ended up being retained on the Hirsch funnel along with the catalyst. In effect, this was the way how the presence of 4a could be confirmed.

Unfortunately, the yields for the synthesis of 6a were not particularly striking. In fact the best results were obtained on using DABCO-A15-A (2.8 mmol/g) with a loading of 5 mol% (entry 13, yield 44 %, Table 2) in methanol solvent at 70 °C whereas Pip-A15 (2.72 mmol/g) gave an identical result at the same molar amount in ethanol solvent at 80 °C (entry 3, Table 2). Attempting the reactions under neat conditions by first allowing malononitrile, the aldehyde and the catalyst to react at 80 °C before adding ammonium acetate and the ketone did not furnish better yields either (entries 15–17, Table 2). When the catalyst with a lower loading was tried (DABCO-A15-B, 2.1 mmol/g) at 70 °C in methanol or at 80 °C in ethanol identical yields (44 %) were attained (entries 18,19, Table 2). On a green note, despite the low yields, the catalyst (DABCO-A15) is metal-free and no toxic solvents are used in its preparation or during the reaction itself.

### 3.4. Expanding the substrate scope

When the aldehyde was varied and the catalyst used was DABCO-A15-A (2.8 mmol/g loading), the yields for the corresponding bicyclic

**Table 2**
Optimization runs for the synthesis of the 5,6-substituted-2-amino-3-cyanopyridine (6a) synthesized from malononitrile (1), *p*-tolualdehyde (2a), c-hexanone (3a) and ammonium acetate (5).



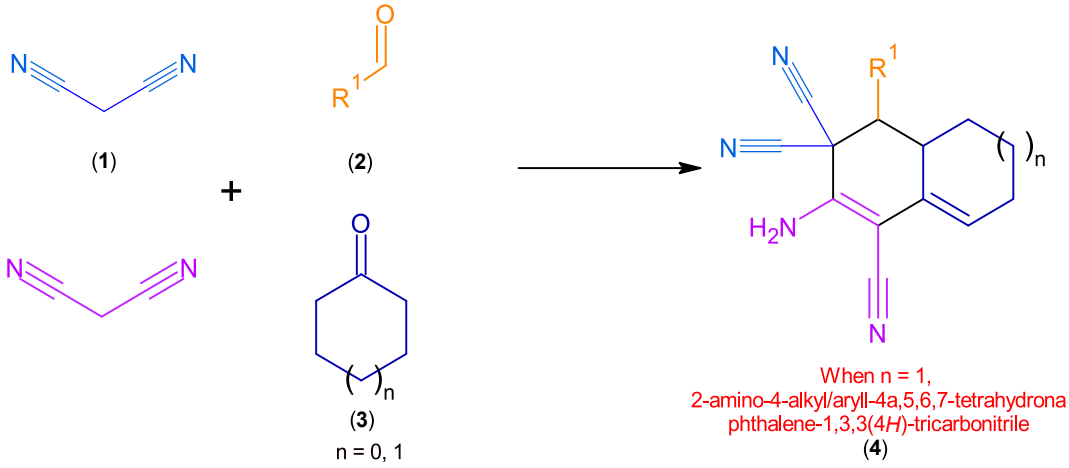

| Entry[a] | Catalyst | Amount of catalyst | Temperature [°C] | Solvent/amount (mL) | Molar Ratio 1 : 2a: 3a: 5 | Yield of 6a/Reaction time (hrs)[b] |
|---|---|---|---|---|---|---|
| 1 | Pip-A15 (2.72 mmol/g) | 5 mol% | 70 | Neat | 1 : 1: 1 : 1.5 | 30 %/1 + 3 |
| 2 | | 5 mol% | 70 | MeOH/4 | 1 : 1: 1 : 1.5 | 38 %/1 + 4 |
| 3 | | 5 mol% | 80 | EtOH/2 | 1 : 1: 1 : 1.5 | 43 %/1 + 4 |
| 4 | | 7.5 mol% | 80 | EtOH/4 | 1 : 1: 1 : 1.25 | 35 %/2 + 3 |
| 5 | | 10 mol% | 60 | EtOH/4 | 1 : 1: 1 : 1.5 | 33 %/2 + 8 |
| 6 | | 10 mol% | 80 | EtOH/4 | 1 : 1: 1 : 1.5 | 16 %/0.25 + 6 |
| 7 | | 10 mol% | 80 | EtOH/4 | 1 : 1: 1 : 1.5 | 40 %/1 + 4 |
| 8 | | 10 mol% | 80 | EtOH/4 | 1 : 1: 1 : 1.5 | 36 %/1 + 3 |
| 9 | | 10 mol% | 80 | EtOH/4 | 1 : 1: 1 : 1.5 | N.A./3[c] |
| 10 | | 10 mol% | 80 | EtOH/4 | 1 : 1: 1 : 1.5 | 10 %/1 + 3[d] |
| 11 | DABCO-A15-A (2.80 mmol/g) | 10 mol% | 80 | EtOH/4 | 1 : 1: 1 : 1.5 | 30 %/1 + 4 |
| 12 | | 10 mol% | 80 | EtOH/4 | 1 : 1: 1 : 1.1 | 40 %/1 + 4 |
| 13 | | 5 mol% | 70 | MeOH/4 | 1 : 1: 1 : 1.5 | 44 %/1 + 4 |
| 14 | | 5 mol% | 80 | EtOH/4 | 1 : 1: 1 : 1.1 | 37 %/1 + 4 |
| 15 | | 10 mol% | 80 | Neat | 1 : 1: 1 : 1.5 | 30 %/1 + 4 |
| 16 | | 5 mol% | 80 | Neat | 1 : 1: 1 : 1.5 | 24 %/1 + 4 |
| 17 | | 3.5 mol% | 80 | Neat | 1 : 1: 1 : 1.5 | 22 %/1 + 4 |
| 18 | DABCO-A15 -B (2.1 mmol/g) | 5 mol% | 70 | MeOH/4 | 1 : 1: 1 : 1.5 | 44 %/1 + 4 |
| 19 | | 5 mol% | 80 | EtOH/4 | 1 : 1: 1 : 1.5 | 44 %/1 + 4 |

[a] Unless otherwise stated, reactions were performed on a 2.5 mmol scale in a stepwise manner by first mixing malononitrile, aldehyde and catalyst in ethanol/methanol solvent and then adding ammonium acetate and ketone.
[b] Unless otherwise stated, product was purified by recrystallization from ethanol and confirmed by IR, $^{1}$H NMR,$^{13}$C NMR.
[c] Reactants were added all at the same time in multicomponent one-pot fashion.
[d] Ammonium acetate and ketone were first mixed along with catalyst and solvent before adding aldehyde and malononitrile.

*ortho*-amino carbonitriles (4) ranged between 10 and 89 % (Table 3) with very good results being obtained on using the electron-poor halogenated aldehydes (entries 7–11) and electron-rich methoxy-substituted aldehydes (Table 3, entries 5, 6). However, one needs to point out that the latter required a longer reaction time to furnish high yields as could be understood from performing the reaction for different reaction times. Interestingly, the electron-poor nitro-substituted aldehydes (Table 3, entries 3, 4) did not perform as good possibly because they were so reactive that they resulted in the formation of other side products as could be attested by other minor spots on the TLC plates developed during reaction monitoring. In fact, when the trial involving 3-nitrobenzaldehyde was performed for longer (6 h instead of 4) the yield actually decreased (Table 3, entry 4). Heteroaromatic aldehydes could also furnish the expected product albeit in poorer yields (Table 3, entries 12, 13). As for the reaction involving the linear aliphatic aldehyde *n*-butyraldehyde (Table 3, entry 14), several side products were formed and in order to isolate the product column chromatography followed by recrystallization was required. Lastly, changing the ketone to cyclopentanone (Table 3, entries 15–16) proved detrimental to the yield especially in the case of 4-fluorobenzaldehyde for which reaction TLC chromatography showed a multitude of spots.

Interestingly, when the same reactions were repeated using DABCO-A15-B (2.1 mmol/g loading) there was a general improvement for all reactions (Table 3) although the general reactivity trend appeared to be kept. Having stated this, it was noted that the reaction involving nitrobenzaldehydes was significantly cleaner (as per TLC) as the yield value can attest (Table 3, entry 3, 4). The reasoning behind this is probably as follows: since less or no "free" DABCO was present within the polymeric

**Table 3**
Substrate scope expansion for the synthesis of bicyclic ortho-amino carbonitriles from an aldehyde, malononitrile and a ketone.




| Entry[a] | $R^1$ | 3 | Yield (%) of 4[b] [Reaction time (hr)] | Yield (%) of 4[c] [Reaction time (hr)] |
|---|---|---|---|---|
| 1 (model) | 4-$CH_3$-Ph-(**2a**) | -$CH_2CH_2CH_2$-(**3a**) | 89 % [5] | 87 % [5] (**4a**) |
| 2 | Ph-(**2b**) | | 83 % [5] | 82 % [5] (**4b**) |
| 3 | 4-$NO_2$-Ph-(**2c**) | | 57 % [2] | 79 % [2] (**4c**) |
| 4 | 3-$NO_2$-Ph-(**2d**) | | 56 % [4]<br>50 % [6] | 80 % [4] (**4d**) |
| 5 | 4-$OCH_3$-Ph-(**2e**) | | 59 % [5]<br>85 % [7] | 86 % [5] (**4e**) |
| 6 | 2-$OCH_3$-Ph-(**2f**) | | 82 % [6] | 85 % [5] (**4f**) |
| 7 | 2,4-$Cl_2$-Ph-(**2g**) | | 65 % [4] | 78 % [5] (**4g**) |
| 8 | 4-F-Ph-(**2h**) | | 80 % [4] | 83 % [5] (**4h**) |
| 9 | 2-Cl-Ph-(**2i**) | | 71 % [5] | 75 % [5] (**4i**) |
| 10 | 4-Cl-Ph-(**2j**) | | 65 % [4] | 72 % [5] (**4j**) |
| 11 | 4-Br-Ph-(**2k**) | | 74 % [5] | 78 % [5] (**4k**) |
| 12 | 4-$C_5H_5N$-(**2l**) | | 40 % [6] | 73 % [5] (**4l**) |
| 13 | 2-Thiofuranyl-(**2m**) | | 73 % [4] | 78 % [5] (**4m**) |
| 14 | *n*-Butyl-(**2n**) | | 8 %[d] [5] | 8 %[d] [7] (**4n**) |
| 15 | **2a** | -$CH_2CH_2$-(**3b**) | 15 % [5] | 35 % [10] (**4o**) |
| 16 | **2e** | | 35 % [6] | 38 % [10] (**4p**) |

[a] Unless otherwise stated all reactions were performed on a 2.5 mmol scale using a molar ratio of aldehyde/malononitrile/ketone of 1 : 2 : 1.
[b] Yields of pure isolated products collected by recrystallization from ethanol on using 10 mol% of DABCO-A15-A (2.8 mmol/g) as catalyst and performing the reaction in ethanol/water (7 : 3) at 85 °C.
[c] Yields of pure isolated products collected by recrystallization from ethanol on using 20 mol% of DABCO-A15-B (2.1 mmol/g) as catalyst and performing the reaction in ethanol at 95 °C.
[d] Product collected after performing column chromatography using hexane/ethyl acetate (9 : 1) as eluent mixture and then purified further by recrystallizing from ethanol.

matrix of DABCO-A15-B, the overall basic strength of the catalyst was lower which means that the possibility of side reaction was also lower. In fact, another noteworthy improvement was made when using the aldehyde 4-pyridinecarboxaldehyde (Table 3, entry 12).

Turning to the synthesis of 5,6-substituted-2-amino-3-cyanopyridines, the yields were generally inferior (Table 4) when compared to those of the corresponding bicyclic *ortho*-amino carbonitrile (Table 3).

### 3.5. Combination of MCRs – MCR$^2$

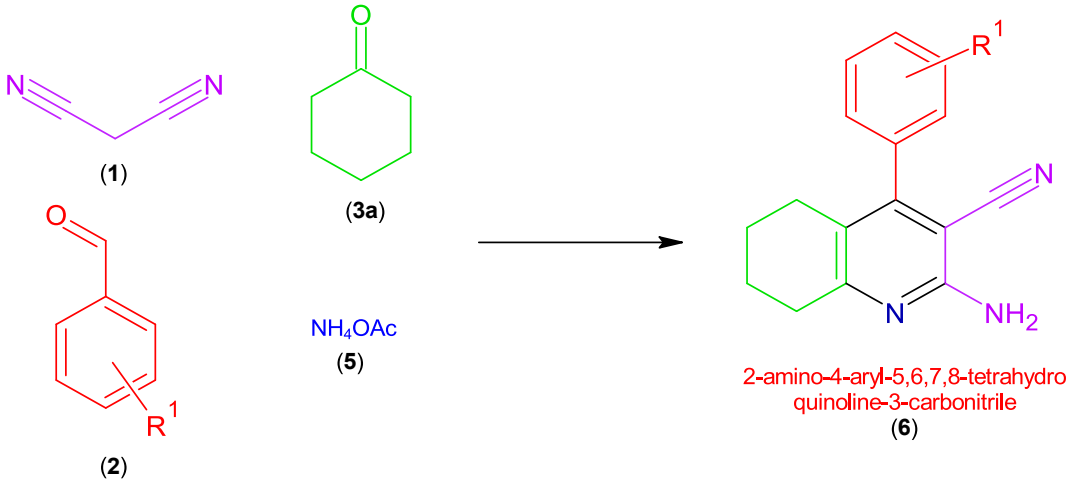
In an innovative unprecedented attempt at combining the skeletal structure of 4 to that of chromenes [25,35], 1-naphthol/2-naphthol (7) was reacted with malononitrile (1) and *p*-terephthaldehyde (2o) in ethanol for 5 h at 80 °C before adding two further equivalents of malononitrile and *c*-hexanone to the same reaction pot (Scheme 5). This approach is a true union of diverse multicomponent reactions under the same reaction conditions in a one-pot combination or shortly MCR$^2$ and the overall result is a pseudo-6-component reaction [36,37]. It must be noted that the catalyst amount had to be increased to 30 mol% to help drive the first part of the reaction. Meanwhile, temperature was lowered to 80 °C to improve chemo selectivity and decrease side product formation. Positively both products (8a, b) could be collected in pure form and were fully characterized.

To the best of the authors' knowledge this has never been conducted before. The relatively poor yield of 8a, b can be partially explained in terms of the fact that final reaction mixture had to be purified by column chromatography and during column loading a certain amount of product crystallized out, never redissolved and ultimately never eluted using hexane/ethyl acetate. Yield improvement was attempted by trying to purify the crude product by recrystallization from ethanol. However, when this was conducted, another side product precipitated out alongside the expected product even when recrystallization was repeated two more times.

### 3.6. Catalyst characterisation

DABCO-A15-B catalyst was characterised by infra-red spectroscopy. In the spectrum of the freshly-prepared catalyst (Fig. 6), the wide band at 3451 cm$^{-1}$ can be attributed to the O–H stretching of any free sulfonic acid groups of A15 or possibly due to the coupled $SO_3$——H——N [DABCO] stretching with the hydrogen being midway in between the two moieties. The minor band at 3211 cm$^{-1}$ is likely to be the N–H bending overtone of 1st harmonic at 1599 cm$^{-1}$. The peak at 3019 cm$^{-1}$ is due to the aromatic C–H stretch whilst those just below 3000 cm$^{-1}$ are because of the aliphatic C–H stretches. From 2801 cm$^{-1}$ up to 2000 cm$^{-1}$, there are minor band due to the coupled stretches of the protonated N–H group [28,38]. Meanwhile, bands at 1466 and 1412 cm$^{-1}$ are caused by the aromatic C–H stretches of the phenyl rings in Amberlyst® 15 and also possibly by the O–H bending of any free sulfonic acid terminals. The band at 1325 cm$^{-1}$ is likely to be due to the S=O stretching of the sulfonate moiety. C–N stretching is possibly represented by the band at 1059 cm$^{-1}$. The band at 1186 cm$^{-1}$ has been

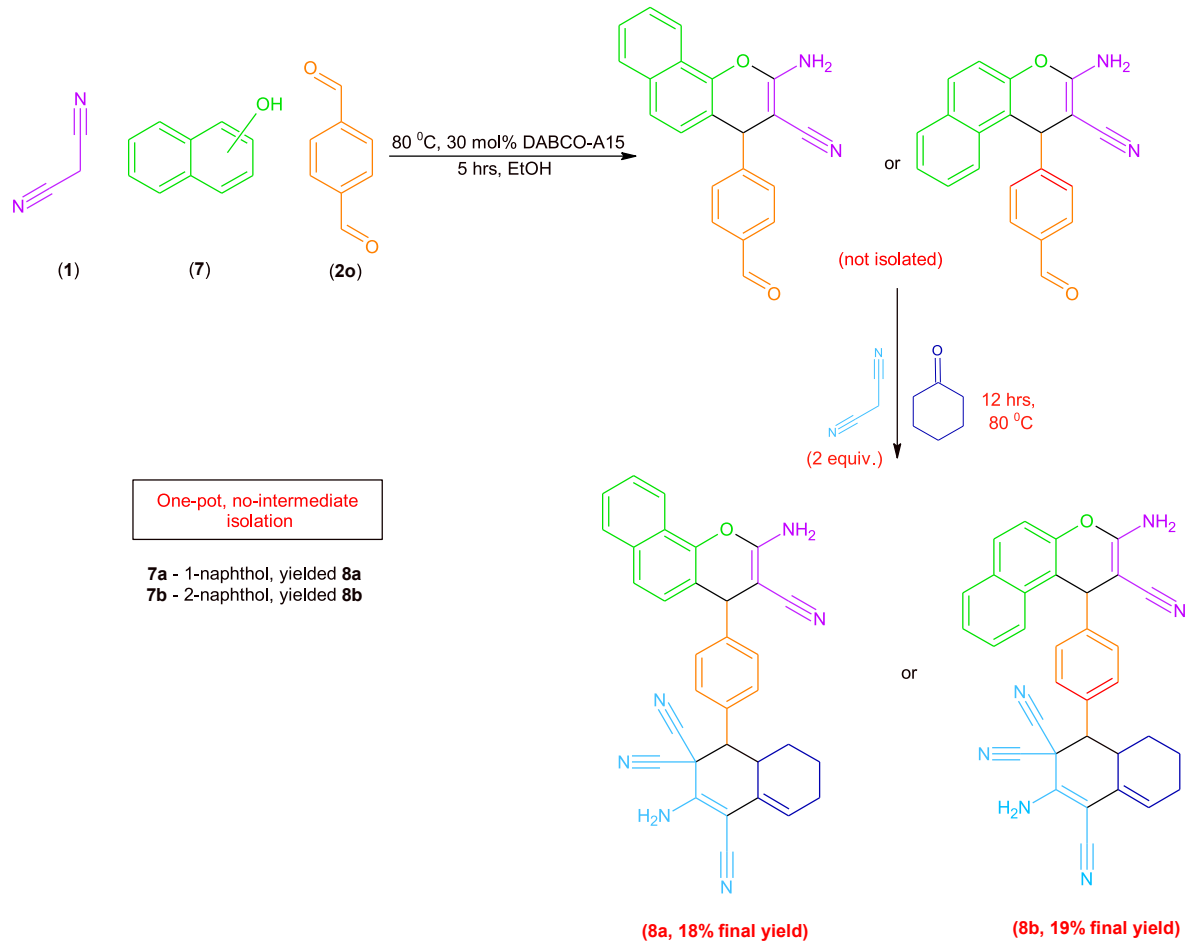
**Table 4**
Substrate scope expansion for the synthesis of 5,6-substituted-2-amino-3-cyanopyridines (6).




| Entry[a] | R$^1$ | Ketone | Reaction time (hrs) | Yield (%) of 6[b] |
|---|---|---|---|---|
| 1 (model) | 4-$CH_3$-Ph (**2a**) | 3a | 1 + 4 | 44 % (**6a**) |
| 2 | Ph (**2b**) | 3a | 1 + 4 | 39 % (**6b**) |
| 3 | 4-$OCH_3$ (**2e**) | 3a | 1 + 20 | 29 % (**6c**) |
| 4 | 4-F-Ph (**2h**) | 3a | 1 + 6 | 28 % (**6d**) |
| 5 | 2-Cl-Ph (**2i**) | 3a | 1 + 6 | 49 % (**6e**) |
| 6 | 4-Br (**2k**) | 3a | 1 + 6 | 28 % (**6f**) |

[a] Unless otherwise stated all reactions were performed on a 2.5 mmol scale using a molar ratio of aldehyde/malononitrile/ketone/ammonium acetate of 1 : 1: 1 : 1.5 at a temperature of 70 °C in 4 mL of methanol using 5 mol% of catalyst DABCO-A15-B. The reaction time is split in two due to the fact that for the first hour only malononitrile and the aldehyde were stirred along with the catalyst.

[b] Yields of pure isolated products collected by recrystallization from ethanol.




**Scheme 5.** Synthesis of complex MCR[2] products.

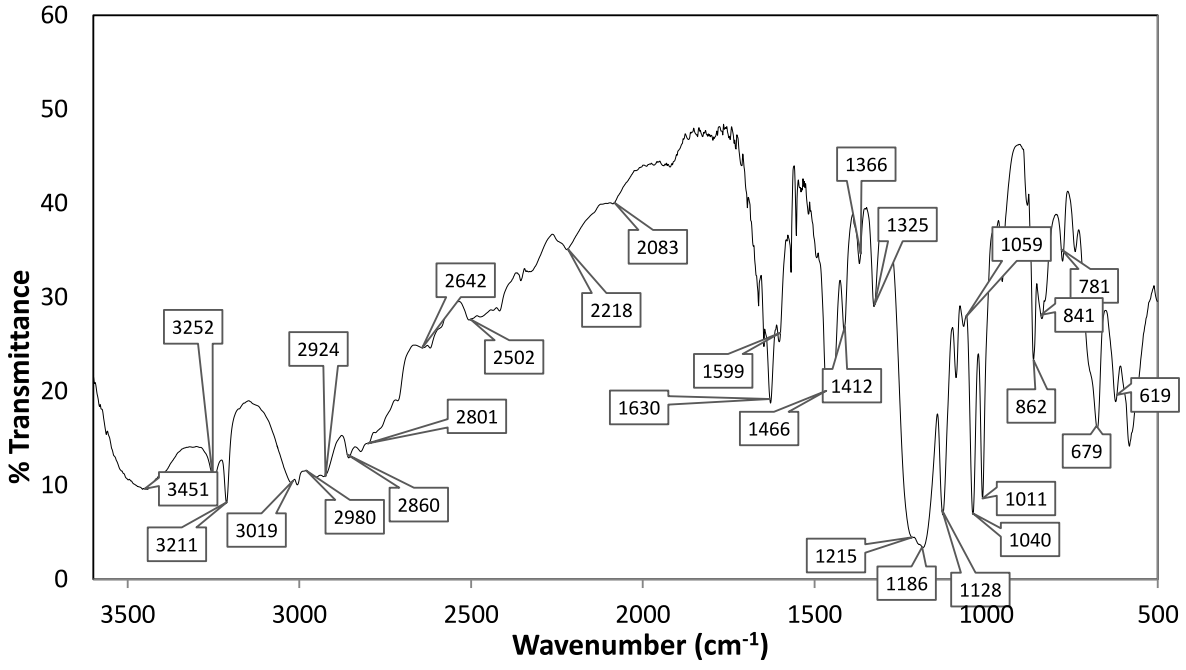



**Fig. 6.** IR spectrum of freshly prepared DABCO-A15-B.

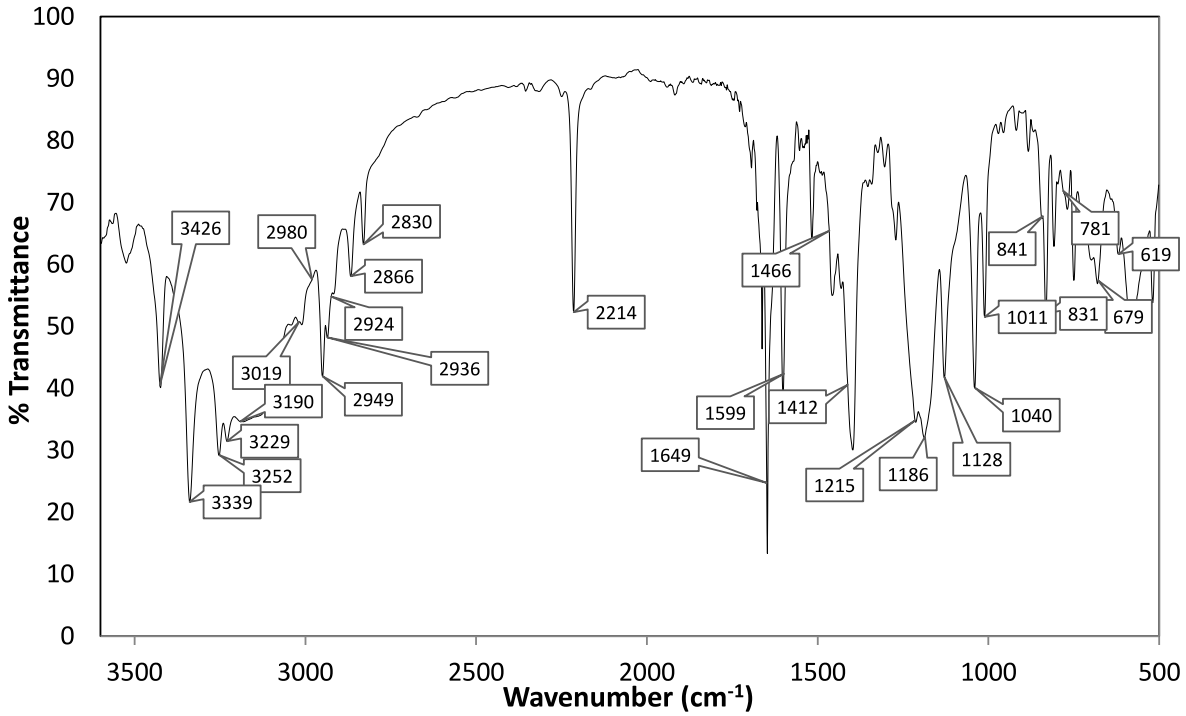



**Fig. 7.** IR spectrum of recycled DABCO-A15-B (after 5th run).

reported in the literature to be attributable to the coupled stretching vibration of the O=S=O group. Close by, the bands at 1128, 1040 and 1011 $cm^{-1}$ are evidence of in-plane skeletal C–H vibrations of a disubstituted benzene ring. A minor band at 781 $cm^{-1}$ is assignable to C–S–C symmetric stretching whereas those at 841, 679 and 619 $cm^{-1}$ are caused by aromatic out-of-plane C–H vibrations [28,38].

The final recycled catalyst IR spectrum (Fig. 7) is practically the same as that in Fig. 6 except for a notably visible nitrile stretch at 2214 $cm^{-1}$ which indicates product adsorption.

### 3.6.1. *Hot filtration test*

In an initial trial, the model reaction for the synthesis of product 4a was performed under optimum conditions using catalyst DABCO-A15-B and then stopped after 30 min. At this point reaction mixture had already turned white due to significant product formation. Hence, acetone (30 mL) was added whilst heating at the same temperature in order to be able to dissolve the product to then filter the catalyst. Meanwhile, the filtrate was concentrated by rotary evaporation, transferred back to a 25-mL 3-neck-round-bottomed flask and left to stir at 95 °C in ethanol (4 mL) for 4.5 h. Subsequently, reaction mixture was worked up and crude product recrystallized from ethanol to ultimately collect the supposed pure product (0.65 g, 85 %). $^1$H NMR analysis however showed that in actual fact this was impure (approximately 15 %) and had the intermediate Knoevenagel product of the aldehyde and malononitrile mixed with it (resulting in a true pure product 6a yield of below 70 %). Surprised by the seemingly fast initial phase of the reaction, the process was repeated but the reaction was stopped after only 3–4 min just about when the first product traces started to precipitate

**Table 5**
Green metrics calculations.

$$Atom\ Economy = \frac{Molecular\ weight\ of\ product}{\sum molecular\ weight\ of\ reactants} \times 100$$
$$= \frac{314.42}{(98.15(c-hexanone) + 120.15\ (tolualdehyde) + 66.06 \times 2(malononitrile)} = 90\%$$

$$E-factor = \frac{total\ mass\ of\ waste}{total\ mass\ of\ product}$$

Total mass of waste = mass of starting materials – (mass of product + mass of recovered catalyst)
Total mass of reactants = 0.0025 x (120.15 + 98.15 + 66.06 + 66.06) = 0.875 g
Total mass of catalyst = 0.24 g (complete mass recovery)
Total mass of solvent = 4 mL * 0.789 g/mL = 3.156 g
Total mass of product = 0.87 × 314.42 x 0.0025 = 0.684 g

Hence,

$$E-factor = \frac{[0.875 + 0.24 + 3.156 - 0.24 - 0.684]}{0.684} = 4.89$$

$$Total\ Process\ Mass\ Intensity = \frac{total\ mass\ of\ starting\ materials}{total\ mass\ of\ product} = \frac{(0.875 + 0.24 + 3.156) + 15.78}{0.684} = 29.31$$

out from the mixture. At this point the reaction was quickly filtered through a previously heated G4 Hirsch funnel and then continued at the same conditions for 5 h. TLC showed minimal product formation and after recrystallization a small amount of product + Knoevenagel intermediate (0.1 g) were ultimately collected. This helped to ascertain that: 1) The reaction truly needs a catalyst to proceed forward and 2) The catalyst DABCO-A15-B does not leach and 3) it operates in a heterogeneous fashion, a property which makes it attractive in light of green chemistry principles [34]. Moreover, the above results help show that the reaction has a very fast initial phase (around 70 % after 30 min) but then the rate decreases significantly with time.

### 3.7. Green metrics

The Atom Economy (AE), the *E*-factor and the Total Process Mass Intensity (PMI) for the model reaction (resulting in the formation of 4a) were calculated as listed in Table 5. All values underline the fact that the reaction is green because it results in minimal waste formation intrinsically (high atom economy) and due to the heterogeneous nature of the catalyst (low E-factor). It must be noted that in the calculation of total process mass intensity, the mass of ethanol (approximately 20 mL, 15.78 g) needed for recrystallization was also included to give the complete picture.

## 4. Conclusion

DABCO-A15 has been shown to be an effective, cheap, easily prepared and recoverable heterogeneous catalyst in the synthesis of bicyclic *ortho*-amino carbonitriles yielding products in appreciably good yields. The method of preparation of the catalyst was found to influence the reaction yields as well as the recyclability. In fact, the catalyst with a lower loading was found to be recyclable for up to 5 runs with an overall yield drop of 14 % whereas that with a higher loading was less reusable. Simultaneously, by replacing one malononitrile equivalent with ammonium acetate, DABCO-A15 helps in the synthesis and pure collection of 5,6-substituted-2-amino-3-cyanopyridines albeit at inferior yields. Finally, a novel approach at synthesizing complex products via a one-pot sequentially combination of multicomponent reactions ($MCR^2$) was adopted successfully.

## CRediT authorship contribution statement

**Giovanna Bosica:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing - review & editing. **Roderick Abdilla:** Conceptualization, Formal analysis, Investigation, Methodology, Software, Writing - original draft.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tgchem.2023.100033.

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