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CHOLINE CHLORIDE CATALYZED ECO-FRIEND AND EFFECTIVE ONE-POT SYNTHESIS OF 9-ARYLACRIDINE-1,8-DIONE AND HEXAHYDROQUINOLINE VIA HANTZSCH TYPE REACTION

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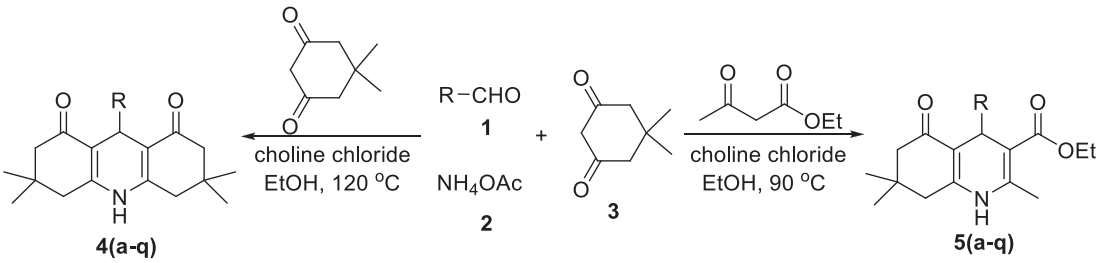
Abstract – Choline chloride was utilized to efficiently catalyzed Hantzsch type reaction for the synthesis of 9-arylacridine-1,8-dione and hexahydroquinoline derivatives. The optimized catalytic system benefits from facile operation and separation procedures, in good to excellent yields, and for wide substrate tolerance. This methodology is of interest also due to employing simple and inexpensive choline chloride as catalyst and environmentally benign ethanol as solvent without the use of any harmful organic solvent and toxic metal catalyst.

Nowadays, developing chemical processes using more eco-friendly acceptable catalysts, reagents, solvents and efficient processes have appeared as subjects of innovation in green chemistry.[1] Deep-eutectic solvents (DES) have drawn increasing attention in recent years due to their less toxic, stable, biocompatible properties and been widely applied as sustainable reaction medium or catalyst in organic synthesis.[2] The formation of DESs results from strong hydrogen bond interactions between hydrogen bond acceptors and hydrogen bond donors such as urea, carboxylic acids, or glycerol.[3] Choline chloride which is simple, non-toxic, and readily available has been utilized as a versatile hydrogen bond acceptor.[4] It is well known that environmentally-friendly ethanol was protic polar solvent[5] and we speculate that it could also play the role of hydrogen bond donor. The combination of choline chloride and protic polar solvent would generate catalytic active species too. Expanding environmentally benign, efficient and economical strategy that employing ethanol as solvent and choline chloride as promoter for the synthesis of important compounds is attractive to our group.

Multi-component reaction (MCR) is a powerful and ideal bond-forming technique in organic, combinatorial, and medicinal chemistry.[6-8] This strategy has greater efficiency with respect to structural complexity and atom economy for the synthesis of diverse chemical libraries in one-pot reactions.[9,10] Development or improvement of the unknown and known MCRs for the synthesis of privileged scaffolds

has received significant attention in recent years.[11-13] Hantzsch type condensation is one of the most prominent MCRs that produces important 1,4-dihydropyridine derivatives. This class of compounds is the key building blocks of numerous nitrogen-containing heterocyclic natural products and represents a "drug-like" structural motif with a broad spectrum of applications in organic synthesis and medicinal chemistry.[14] In view of these useful properties, a good number of methods have been developed to synthesize polyfunctionalized 1,4-dihydropyridine heterocycles by the one-pot multi-component strategy of aromatic aldehyde with 1,3-dicarbonyl compounds and ammonium acetate.[15] However, the catalysts employed in most of these reactions are not always cheap, simple, and eco-friendly. Thus, the development of more green, general, efficient, feasible, high yielding, and cost effective methods for the synthesis of this class of compounds is highly desirable.[16] As a continuation of our research devoted to the development of green organic transformations and one-pot multi-component reactions for the synthesis of various heterocyclic compounds,[17] herein, we wish to demonstrate that the combination of ethanol and catalytic amount of choline chloride is an effective and environmentally friendly reacted system in the synthesis of 1,4-dihydropyridine derivatives acridine-1,8-diones and hexahydroquinolines via Hantzsch type reaction.



Scheme 1. The approach for the preparation of acridine-1,8-diones and hexahydroquinolines

In our initial endeavours, ammonium aetate, dimedone and benzaldehyde (mole ratio 1.5:2:1) were selected as model substrates to investigate the feasibility of this reaction system (Table 1). As we expected, the product **4a** was furnished in a satisfactory yield in protic polar solvents such as MeOH, EtOH and *i*-PrOH (Table 1, Entries 1~3). But we were surprised to note that glycerol gave a poor outcome for this reaction (Table 1, Entry 4) and reaction in water afforded xanthenedione as the main product (Table 1, Entry 5). Therefore, EtOH was used as the most appropriate reaction medium with its low toxicity and higher yield. Next, two comparison experiments were tested with triethylbenzylammonium chloride (TEBAC) or tetrabutylammonium bromide (TBAB) as promoter (Table 1, Entries 6, 7). It was found that the catalytic ability of choline chloride was superior to other quaternary ammonium salt. To achieve the best reaction conditions, the model reaction was carried out in different temperature, time and molar ratio of ammonium acetate. As shown in Table 1, increasing or decreasing the molar ratio of ammonium acetate failed to improve the result (Table 1, Entries 8, 9) and

reaction at 120 °C for 3 h could offer the target molecule with 92% yield (Entry 12). Further screening showed that decreasing the catalyst amount to 10 mol% could lead to a slightly higher yield of 93% (Table 1, Entry 13). However, the product yield dropped to 89% by further decreasing the catalyst to 5 mol% (Table 1, Entry 14). Thus, the reaction was optimized using cheap, safe, and environmentally benign reaction medium and catalyst.

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

Entry[a]	Catalyst/mol%	Solvent	Temp./°C	Time/h	Yield[b]/%
1	choline chloride 30%	MeOH	120	5	85
2	choline chloride 30%	*i*-PrOH	120	5	88
3	choline chloride 30%	EtOH	120	5	92
4	choline chloride 30%	glycerol	120	5	76
5	choline chloride 30%	H_2O	120	5	19
6	TEBAC 30%	EtOH	120	5	84
7	TBAB 30%	EtOH	120	5	89
8[c]	choline chloride 30%	EtOH	120	5	91
9[d]	choline chloride 30%	EtOH	120	5	84
10	choline chloride 30%	EtOH	110	5	91
11	choline chloride 30%	EtOH	120	2	90
12	choline chloride 30%	EtOH	120	3	92
13	choline chloride 10%	EtOH	120	3	93
14	choline chloride 5%	EtOH	120	3	89

[a] Reaction condition: 0.5 mmol benzaldehyde, 0.75 mmol ammonium acetate, and 1.0 mmol dimedone. [b] Isolated yields. [c] 0.85 mmol ammonium acetate. [d] 0.5 mmol ammonium acetate.

Table 2. Scope of substrate for the synthesis of **4**

Entry[a]	R	Product	Yield[b]/%	Mp/°C
1	C_6H_5	**4a**	93	287-294 (277-279[15c])
2	4-MeC_6H_4	**4b**	94	>300 (>300[17d])
3	3-MeC_6H_4	**4c**	92	>300 (303-305[17d])
4	2-MeC_6H_4	**4d**	92	>300 (>299-302[17d])
5	4-$MeOC_6H_4$	**4e**	93	299-300 (278-280[15c])
6	3-$MeOC_6H_4$	**4f**	90	>300 (>300[17d])
7	2-$MeOC_6H_4$	**4g**	87	296-298 (>300[15e])
8	4-ClC_6H_4	**4h**	98	296-299 (>300[15e])
9	3-ClC_6H_4	**4i**	93	>300 (283-285[15e])
10	2-ClC_6H_4	**4j**	95	300-303 (263-264[15e])
11	4-BrC_6H_4	**4k**	96	>300 (>300[17d])
12	3-BrC_6H_4	**4l**	93	>300 (294-297[15e])
13	2-BrC_6H_4	**4m**	97	>300 (>300[17d])
14	4-$NO_2C_6H_4$	**4n**	83	270-288 (302-304[17d])
15	3-$NO_2C_6H_4$	**4o**	96	305-313 (293-295[17d])
16	2-$NO_2C_6H_4$	**4p**	79	293-295 (297-299[17d])
17	isopropyl	**4q**	86	285-286 (283-284[15a])

[a] Reaction condition: 0.5 mmol benzaldehyde, 0.75 mmol ammonium acetate, 1.0 mmol dimedone and 0.05 mmol choline chloride, 120 °C, 3 h. [b] Isolated yields.

With the optimized conditions in hand, we turned our attention to check the generality as well as the effectiveness of our newly developed protocol. Various aromatic aldehydes having different substituent were employed, and the reaction proceeded smoothly to give the desired products **4a**-**4p** in good to excellent yields (Table 2). The presence of electron donating substituent or weakly electron withdrawing group in the ortho, meta or para positions on the ring of aromatic aldehyde seemed to have little influence on the yield values. Unfortunately, poor yields were obtained when nitro group was present in ortho or para positions of phenyl ring (Table 2, Entries 14, 16). However, employing 3-nitrobenzaldehyde as substrate gave a satisfactory result (Table 2, Entry 15). This outcome showed that introducing strongly electron-withdrawing group in ortho or para positions of phenyl ring would decrease the yield. In other words, the electron deficient benzaldehyde which containing an overactive carbonyl group was disfavored to the reaction.

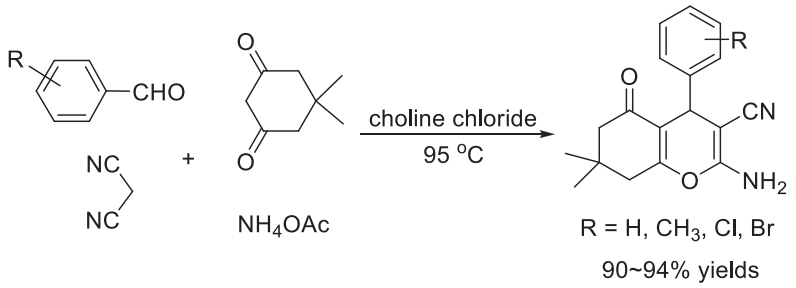
Inspired by the catalytic potential of choline chloride, we replaced the substrate from dimedone to ethyl acetoacetate and repeated the reaction with the same substituted aldehydes (Scheme 1). Compared with the initial reaction utilizing dimedone, the reactions produced the corresponding hexahydroquinoline in slightly high yields at 90 ºC for 3.5 h. The nature of the aldehyde substituents also showed no significant effect on the yields (Table 3). However, aliphatic aldehydes afforded moderate yields in this two reaction system.

Table 3. Scope of substrate for the synthesis of product **5**

Entry[a]	R	Product	Yield[b]/%	Mp/ºC
1	C_6H_5	**5a**	96	229-234 (218-220[17d])
2	4-MeC_6H_4	**5b**	93	282-286 (260-262[15f])
3	3-MeC_6H_4	**5c**	94	246-253 (230-231[17d])
4	2-MeC_6H_4	**5d**	95	218-232 (203-205[17d])
5	4-$MeOC_6H_4$	**5e**	91	264-271 (255-257[15d])
6	3-$MeOC_6H_4$	**5f**	90	223-226 (199-200[15b])
7	2-$MeOC_6H_4$	**5g**	95	265-269 (247-248[17d])
8	4-ClC_6H_4	**5h**	93	261-264 (243-245[15b])
9	3-ClC_6H_4	**5i**	95	218-220 (205-207[17d])
10	2-ClC_6H_4	**5j**	96	215-217 (207-210[15b])
11	4-BrC_6H_4	**5k**	96	269-271 (252-254[15f])
12	3-BrC_6H_4	**5l**	97	209-211 (196-198[17d])
13	2-BrC_6H_4	**5m**	97	225-227 (192-194[15f])
14	4-$NO_2C_6H_4$	**5n**	81	243-256 (240-242[15d])
15	3-$NO_2C_6H_4$	**5o**	91	188-189 (182-184[15d])
16	2-$NO_2C_6H_4$	**5p**	94	183-187 (207-209[15d])
17	isopropyl	**5q**	72	159-162 (157-158[16b])

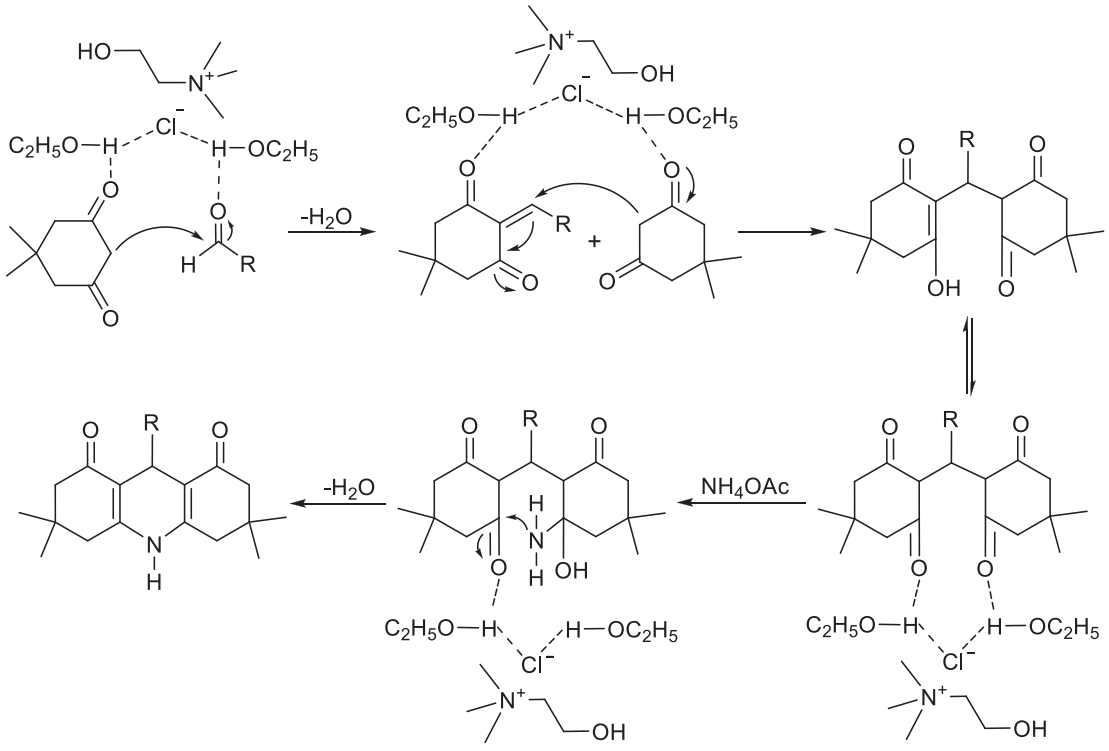
[a] Reaction condition: 0.5 mmol benzaldehyde, 0.75 mmol ammonium acetate, 0.5 mmol dimedone, 0.5 mmol ethyl acetoacetate and 0.05 mmol choline chloride, 90 ºC, 3.5 h. [b] Isolated yields.

To expand the reaction scope, we also tried the reaction by replacing ethyl acetoacetate with malononitrile. As some literature reported,[18] the corresponding tetrahydrobenzo[*b*]pyrans were obtained instead of polyhydroquinolines in anhydrous ethanol (Scheme 2). We also found that adding a little water could improve the reaction and afford high yields.



Scheme 2. The four component approach for replacing ethyl acetoacetate with malononitrile

The plausible mechanism of this reaction was proposed in Scheme 3. Initially, the benzylidenedimedone formed via Knoevenagel condensation of aldehyde and dimedone which were facilitated through hydrogen bonding between choline chloride and the oxygen of carbonyl groups. Then, Michael addition of another dimedone to benzylidenedimedone gave tetraketone. Finally, the nucleophilic attack of nitrogen to carbon group led to the desired product with the elimination of water.



Scheme 3. The possible mechanism for the formation of acridine-1,8-dione

In summary, we have studied the catalytic ability of choline chloride as a mild, environmentally benign, economical and efficient catalyst for the multi-component synthesis of 9-arylacridine-1,8-dione and hexahydroquinoline derivatives with good to excellent yields in ethanol. Broad substrate scope, non-toxic and widely available catalyst, environmentally benign solvent and easy purification are the most attractive merits of this methodology.

EXPERIMENTAL

Commercial solvents and reagents were used directly as received materials, except for benzaldehyde, which was used as freshly distilled sample. Melting points were measured on Beijing Tech X-5 melting point detector and were uncorrected. FT-IR spectra were determined on a Bruker Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 MHz.

General procedure for synthesis of 9-arylacridine-1,8-diones 4a-q.

0.05 mmol Choline chloride and 1 mL EtOH were added to a 10 mL pressure tube and stirred at 120 ^{o}C for 10 min. Then aldehyde (0.5 mmol), dimedone (1 mmol), and ammonium acetate (0.75 mmol) were added. This mixture was heated at 120 ^{o}C for 3 h. After completion of the reaction, 1 mL water was added and continuously stirred for a moment at 120 ^{o}C. Finally, the mixture was left to cool in ice bath and filtered to afford the desired 9-arylacridine-1,8-dione without further purification.

General procedure for the synthesis of hexahydroquinolines 5a-q.

0.05 mmol Choline chloride and 1 mL EtOH were added to a 10 mL pressure tube and stirred at 90 ^{o}C for 10 min. Then the corresponding aldehyde (0.5 mmol), dimedone (0.5 mmol), ethyl acetoacetate (0.5 mmol), and ammonium acetate (0.75 mmol) were added. This mixture was heated at 90 ^{o}C for 3.5 h and 1 mL water was added upon completion of the reaction. Finally, the mixture was left to cool in ice bath and was filtered to afford the desired hexahydroquinoline without further purification.

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