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# Synthesis of polysubstituted pyridines under combined microwave and ultrasound irradiation: $K_2CO_3$-promoted tandem addition/cyclization/hydrogen shift process

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ABSTRACT

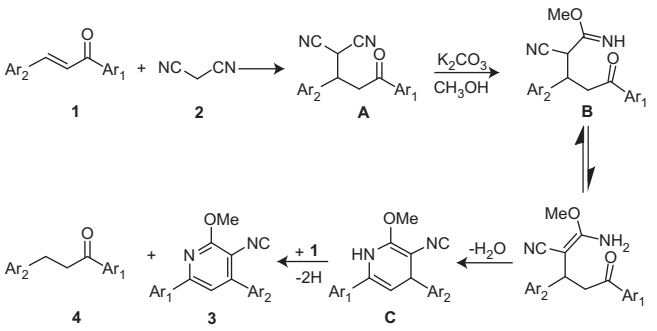
A convenient and efficient $K_2CO_3$-promoted tandem reaction of chalcone, malononitrile, and methanol for the synthesis of highly functionalized pyridines has been developed. This multi-component reaction employing the weak nucleophilic agent methanol proceeded smoothly under combined microwave and ultrasound irradiation (CMUI). The reaction mechanism was proposed to consist of a Michael addition, a methoxylation of C≡N bond, a cyclization to a 1,4-dihydropyridine and an intermolecular hydrogen shift between 1,4-dihydropyridine and initial chalcone.



Pyridines are frequently encountered as skeletal components and valuable functional moieties of many biologically active compounds and natural products.[1] Therefore, the development of efficient methods to facilitate the synthesis of pyridines has currently attracted much attention in both academia and industry.[2] During recent years, one-pot multi-component reactions (MCRs) as well as domino processes provide synthetic efficiency, intrinsic atom economy, and procedural simplicity to construct highly complex molecules.[3] Meanwhile, microwave- and ultrasound-assisted organic synthesis has been developed and well documented, owing to the fact that these technologies can usually reduce the reaction times, minimize energy consumption, and in certain cases, increase the yield and selectivity of product formation.[4]

In view of the multi-component synthesis of pyridines,[5] we focused our attention on the three-component condensation of a chalcone, malononitrile, and a nucleophilic agent for the synthesis of 4,6-diaryl-2-methoxynicotinitriles. Various nucleophilic agents such as amines,[6] benzenethiols,[7] alkoxides[8] have been used to perform a nucleophilic attack at one of the nitrile groups of malononitrile. However, the application of a weak nucleophilic agent such as methanol often resulted in low yields of the target product even in the presence of a strong base such as NaOH, KOH, or Na.[9] As part of our continuing efforts to explore the application of combined microwave and ultrasound irradiation (CMUI) in heterogeneous organic reactions,[10] we found that CMUI could strongly accelerate the synthesis of 4,6-diaryl-2-methoxynicotinitriles, applying the weak nucleophilic methanol in the presence of the weak base $K_2CO_3$ without the addition of any oxidant. To the best of our knowledge, there are no example describing the formation of 4,6-diaryl-2-methoxynicotinitriles employing a weak base. However, the chalcone is else acting as an efficient reaction promoter via the hydrogen shift between chalcone and 1,4-dihydropyridine intermediate (Scheme 1, C).

In an initial investigation, we employed chalcone **1j**, malononitrile, and methanol as nucleophilic agent in the presence of different bases under CMUI. The reactions were performed at




**Scheme 1.** Proposed mechanism for the protocol.

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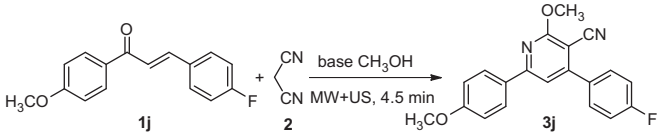
**Table 1**
Optimization of the conditions[a]




| Entry | **1a**/**2** (mmol) | Base (equiv) | Oxidant (equiv) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | 1:1 | $Na_2CO_3$ (1.5) | — | 38 |
| 2 | 1:1 | $K_2CO_3$ (1.5) | — | 43 |
| 3 | 1:1 | $K_2CO_3$ (2.5) | — | 45 |
| 4 | 1:1 | $K_2CO_3$ (3) | — | 45 |
| 5 | 1:1 | NaOH (3) | — | 48 |
| 6 | 1:1 | KOH (3) | — | 50 |
| 7 | 1:1 | $NEt_3$ (3) | — | 10 |
| 8 | 1:1 | Pyridine (3) | — | 8 |
| 9 | 1:1 | Piperidine (3) | — | 16 |
| 10 | 1:1 | $K_2CO_3$ (1.5) | DDQ (1.5) | 36 |
| 11 | 1:1 | $K_2CO_3$ (1.5) | $H_2O_2$ (2) | 22 |
| 12 | 1:1 | $K_2CO_3$ (1.5) | $MnO_2$ (2.5) | 40 |
| 13 | 1:1 | $K_2CO_3$ (1.5) | $FeCl_3$ (2) | 7 |
| 14 | 1.5:1 | $K_2CO_3$ (1.5) | — | 78 |
| 15 | 1.8:1 | $K_2CO_3$ (1.5) | — | 84 |
| 16 | 2:1 | $K_2CO_3$ (1.5) | — | 85 |
| 17 | 2:1 | $K_2CO_3$ (1.5) | — | 64[c] |

[a] Reactions were performed under reflux using malononitriles (1.0 mmol) and methanol (6 mL) for 4.5 min. CMUI (microwave: 100 W; ultrasound: 50 W).
[b] Conversion based on malononitriles.
[c] Conventional heating under reflux conditions for 6 h.

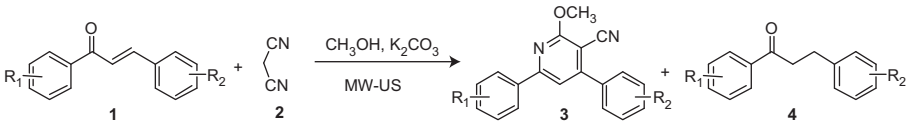
reflux for 4.5 min. The desired product **3j** was easily isolated by filtration. Among the bases tested, all of the inorganic and organic bases led to unsatisfactory results (Table 1, entries 1–9), as the yields did not exceeded 50%. Interestingly, only a slightly lower yield was obtained when the relatively weak base $K_2CO_3$ was used (Table 1, entries 1–6). In an attempt to improve the yield, we executed the reactions in the presence of a known 1,4-dihydropyridine oxidizing agent such as DDQ,[11] $H_2O_2$,[12] $MnO_2$[13], or $FeCl_3$.[14] However, it was found that none of them had positive effect (Table 1, entries 10–13). Analysis of the filtrate showed the appearance of 3-(4-fluorophenyl)-1-(4-methoxyphenyl) propan-1-one **4j**. It provided us the clue that compound **4j** may be formed via intermolecular hydrogen shift between chalcone **1j** and 1, 4-dihydropyridine the intermediate for the formation of product **3j**.[15] To examine the feasibility of this hydrogen shift reaction, more than the stoichiometric ratio of chalcone **1j** was used (Table 1, entries 14–16). To our delight, when the amount of chalcone **1a** was increased to 1.8 equiv, product **3j** was obtained in an 84% yield together with the corresponding reduction product **4j** (Table 1, entry 15). Increasing the amount of chalcone to 2 equiv resulted in only a slight increase of the yield of **3j** (Table 1, entry 16). This investigation indicated that apart from the participation in the main reaction, chalcone **1j** was also acting as an efficient hydrogen acceptor which played a key role to increase the yield of desired product. Interestingly, under conventional heating the desired product **3j** was obtained in a moderate yield of 64% after refluxing for 6 h (Table 1, entry 17). The dramatic increase in reaction rate under combined microwave and ultrasound irradiation could be ascribed to the simultaneous intensive enhancements of both heat and mass transfer.

Having the optimized conditions at hand (Table 1, entry 16), we next evaluated the tandem addition/cyclization/hydrogen shift process of various chalcones with malononitrile and methanol. As listed in Table 2, all reactions went on smoothly and quickly under CMUI. Both electron-rich and electron-deficient chalcones **1** provided the desired product **3** in good yields. In addition, the 1,3-diphenylpropan-1-ones **4**, could be obtained in moderate yields of 40–61% (Table 2).

Based on the previous work[6a] and our present results, a mechanism for the formation of products **3** and **4** is proposed (Scheme 1). Upon Michael addition of chalcones **1** with malononitrile **2** compounds **A** are formed. Nucleophilic addition of methanol to the C≡N bond of the adduct gives intermediate **B**. Dehydrative cyclization of **B** affords dihydropyridine **C.** Subsequently the important step is that intermolecular hydrogen shift from **C** to chalcone **1** produces the desired products **3** and **4**.[7a,15]

In conclusion, we have successfully developed an efficient methodology for the preparation of poly-substituted pyridines via a $K_2CO_3$-promoted multi-component tandem reaction of

**Table 2**
Scope and limitations of the protocol[a]




| Entry | $R_1$ | $R_2$ | Time (min) | Product **3** | Yield[b] (%) | Product **4** | Yield[b] (%) |
|---|---|---|---|---|---|---|---|
| 1 | H | 3,4-O-$CH_2$-O– | 4 | **3a** | 81 | **4a** | 56 |
| 2 | H | 4-F | 5 | **3b** | 82 | **4b** | 58 |
| 3 | 4-Cl | 4-$CH_3O$ | 2 | **3c** | 82 | **4c** | 57 |
| 4 | 4-$CH_3$ | 3,4,5-$(CH_3O)_3$ | 5 | **3d** | 90 | **4d** | 41 |
| 5 | 4-$CH_3$ | 4-$CH_3O$ | 6 | **3e** | 71 | **4e** | 52 |
| 6 | 4-$CH_3$ | 4-F | 4 | **3f** | 82 | **4f** | 54 |
| 7 | 4-$CH_3$ | 4-$CH_3$ | 4.5 | **3g** | 74 | **4g** | 50 |
| 8 | 4-$CH_3$ | 4-$CH(CH_3)_2$ | 5.5 | **3h** | 75 | **4h** | 49 |
| 9 | 4-$CH_3O$ | 3,4,5-$(CH_3O)_3$ | 4 | **3i** | 83 | **4i** | 45 |
| 10 | 4-$CH_3O$ | 4-F | 4.5 | **3j** | 85 | **4j** | 53 |
| 11 | 4-$CH_3O$ | 3-Br | 5 | **3k** | 79 | **4k** | 40 |
| 12 | 4-$CH_3O$ | 4-$CH_3$ | 4.5 | **3l** | 73 | **4l** | 61 |
| 13 | 4-$CH_3O$ | H | 5 | **3m** | 86 | **4m** | 43 |
| 14 | 4-$CH_3O$ | 4-$CH_3O$ | 4.5 | **3n** | 82 | **4n** | 52 |

[a] A mixture of chalcones (2.0 mmol), malononitrile (1.0 mmol), $K_2CO_3$ (1.5 mmol), and methanol (6 mL) was subjected to CMUI (microwave: 100 W; ultrasound: 50 W) for the indicated time (monitored by TLC) under reflux.
[b] Isolated yields.

chalcone, malononitrile, and methanol under CMUI.[16] The formation of the final pyridine via intermolecular hydrogen shift from 1,4-dihydropyridine to chalcone is more effective than applying a standard oxidant. Moreover, our results prove that the strong base can be successfully replaced by $K_2CO_3$ without a additional oxidant, and good yield of the desired product is obtained.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.103.

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16. *General procedure for the synthesis of 4,6-diaryl-2-methoxy-nicotinonitriles* ***3*** *and 1,3-diarylpropan-one* ***4***: A mixture of chalcones **1** (2 mmol) and malononitrile **2** (1 mmol) in methanol (6 mL) with $K_2CO_3$ (1.5 mmol) was subjected to microwave–ultrasound activation condition. The ultrasound and microwave source are switched on successively (power level: ultrasound 50 W, microwave 100 W). The mixture was irradiated simultaneously by microwaves and ultrasound for 4–6 min. The suspension was filtered, the residue was washed with water and methanol, after which the residue was dried under vacuum to obtain the products **3**. Water and methanol were evaporated and the residue was redissolved in $CH_2Cl_2$. The solution dried over anhydrous $Mg_2SO_4$, filtered. The resulting reaction mixture was loaded on a column and flashed on silica gel (12–15% EtOAc/petroleum) to afford the desired product **4**.