Microwave-Assisted Improved Synthesis of Pyrrolo[2,3,4-kl]acridine and Dihydropyrrolo[2,3,4-kl]acridine Derivatives Catalyzed by Silica Sulfuric Acid

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Abstract: An improved synthesis of multifunctionalized pyrrolo[2,3,4-kl]acridine derivatives with different substituted patterns using silica sulfuric acid (SSA) as a heterogeneous catalyst under microwave irradiation conditions was developed. The reaction could be conducted by using readily available and inexpensive substrates within short periods of 12–15 min. under microwave irradiation. Compared with the conventional methods, the remarkable advantages of this method are milder reaction conditions, operational simplicity, higher yields, short reaction times, and an environmentally friendly procedure.

Keywords: pyrrolo[2,3,4-kl]acridine; silica sulfuric acid; microwave irradiation
1. Introduction

Acridine derivatives were primarily used as stains for dye manufacturing (e.g., acridine orange) until their fluorescence and chemiluminescence properties found numerous other applications [1–3]. Such acridines have demonstrated important biological activity [4], including activity against cancer [5] due to their ability to intercalate into DNA and disrupt unwanted cellular processes [6]. This unique property of acridines has been exploited in many areas of medicine. As a result, significant biological activity toward viruses [7], bacteria [8], parasites [9,10], fungus [11], Alzheimer’s disease [12], and HIV/AIDS [13] has also been reported. Pyrrolo[2,3,4-kl]acridine derivatives have been isolated from a *Plakortis* sponge and showed biological activities [14,15]. Although there have been some reports on the synthesis of these molecules [16,17], those methods require multistep syntheses. Recently, we [18] and Tu [19] reported the one-pot synthesis of pyrrolo[2,3,4-kl]acridine derivatives catalyzed by L-proline or AcOH, respectively. However, these methods required the use of toluene or acetic acid as solvents. Thus, there is a need for the development of concise and green methods for the construction of this heterocyclic skeleton.

The need to reduce the amount of toxic waste and by-product arising from chemical process requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods. One of the most promising approaches in organic synthesis is the use of reusable heterogeneous catalysts because of their environmental, economical, and industrial aspects [20]. The development of efficient methods using recoverable and reusable catalysts is an important goal in organic synthesis. Up to now, several reusable and heterogeneous catalysts have been designed and used. One useful example is silica sulfuric acid (SSA), which has been widely studied in recent years [21–23], in a variety of reactions such as cross-Aldol condensation [24], deacylation [25], selective oxidation [26], Michael addition [27] and functional group protection [28]. In our previous works, SSA was used as an efficient catalyst for the acetylation of aldehydes and sugars [29]. As a continuation of our interest in organic reactions catalyzed by solid acids [29,30], herein, we report the microwave-assisted green synthesis of pyrrolo[2,3,4-kl]acridine-1-one derivatives catalyzed by SSA in ethanol.

2. Results and Discussion

In a preliminary study, we optimized the reaction conditions, including reaction solvents, temperature, catalyst and amount of SSA catalyst using isatin (1a), and 3-(4-tert-butylphenylamino)-5,5-dimethylcyclohex-2-enone (2a) as model reactants (Scheme 1). The reaction mixture, which was composed of a 1:1 mixture of 1a to 2a, was tested under different conditions. The results are summarized in Table 1.
Table 1. Optimization of the reaction conditions for the synthesis of 3a.

| Entry | Solvent       | Catalyst       | T (°C) | Time (min) | Yield a (%) |
|-------|---------------|----------------|--------|------------|-------------|
| 1     | ethanol       | -              | 110    | 15         | 23          |
| 2     | ethanol       | SSA (0.02 g)   | 110    | 15         | 91          |
| 3     | AcOH          | SSA (0.02 g)   | 110    | 15         | 85          |
| 4     | H2O           | SSA (0.02 g)   | 110    | 15         | 81          |
| 5     | ethylene glycol | SSA (0.02 g) | 110    | 15         | 87          |
| 6     | toluene       | SSA (0.02 g)   | 110    | 15         | 91          |
| 7     | ethanol       | HCl (0.5 mL)   | 110    | 15         | 78          |
| 8     | ethanol       | H2SO4 (0.5 mL) | 110    | 15         | 59          |
| 9     | ethanol       | I2 (0.02 g)    | 110    | 15         | 73          |
| 10    | ethanol       | L-proline (10 mol%) | 110 | 15 | 40 |
| 11    | ethanol       | SSA (0.03 g)   | 110    | 15         | 90          |
| 12    | ethanol       | SSA (0.04 g)   | 110    | 15         | 91          |
| 13    | ethanol       | SSA (0.01 g)   | 110    | 15         | 76          |
| 14    | ethanol       | SSA (0.02 g)   | 90     | 15         | 71          |
| 15    | ethanol       | SSA (0.02 g)   | 100    | 15         | 85          |
| 16    | ethanol       | SSA (0.02 g)   | 120    | 15         | 87          |
| 17    | ethanol       | SSA (0.02 g)   | 110    | 8          | 77          |
| 18    | ethanol       | SSA (0.02 g)   | 110    | 10         | 87          |
| 19    | ethanol       | SSA (0.02 g)   | 110    | 12         | 91          |
| 20    | ethanol       | SSA (0.02 g)   | 110    | 20         | 89          |

a Yield was determined by HPLC-MS.

The optimization process revealed that the reactions did not proceed in ethanol under catalyst-free conditions (Table 1, entry 1). Pleasingly, the target compound 3a was obtained in ethanol with 0.02 g SSA as catalyst (Table 1, entry 2). To improve the yield, different solvents were evaluated. The results indicated that ethanol provided much better results than AcOH, ethylene glycol or water (Table 1, entries 2–5). The non-polar solvent toluene gave the same yield (Table 1, entry 6). Considering the toxicity of toluene, ethanol was selected as the preferred reaction solvent. Several other catalysts were also evaluated for their catalytic efficiency in the current reaction. Common acids (H2SO4 and HCl) and other catalysts (I2 or L-proline) can catalyze this reaction with low yields (Table 1, entries 7–10). The results revealed that SSA was the optimal catalyst with the product being isolated in 91% yield (Table 1, entry 2). Subsequently, we proceeded to evaluate the amount of SSA required for this reaction. When 0.02 g of silica gel was used, the reaction of 3a proceeded in good yield (91%, Table 1, entry 2). The reaction yield remained unchanged when we increased the amount of SSA (Table 1, entries 11 and 12), but the yield was lower when the amount of SSA was decreased (Table 1, entry 13), therefore, 0.02 g of SSA is sufficient to initiate the reaction. To identify the optimum reaction temperature, the reaction was carried out with 0.02 g SSA at 90 °C, 100 °C, 110 °C and 120 °C, providing the product 3a in yields of 71%, 85%, 91% and 87% (Table 1, entries 14, 15, 2 and 16), respectively, so the most suitable reaction temperature for this reaction is 110 °C. Finally, to optimize the reaction time, the reaction was carried out with 0.02 g SSA at 110 °C and the reaction time used was 8 min, 10 min, 12 min, 15 min and 20 min, respectively. It was found that the reaction can proceed smoothly in 12 min (Table 1, entry 19), while prolonging the reaction time did not enhance the yield of the product (Table 1, entries...
2 and 20). Thus, the optimum conditions required the use of 0.02 g SSA as catalyst in ethanol as solvent at 110 °C and a reaction time of 12 min.

Having established the optimal conditions we proceeded to investigate the substrate scope of the transformation. As shown in Table 2, substituents such as bromo, chloro, fluoro on the isatin ring, and tert-butyl or phenyl groups bearing either electron-withdrawing or electron-donating groups on the enaminone ring, were well tolerated under these reaction conditions, leading to the final products in satisfactory yields (up to 93%).

Table 2. Synthesis of dihydropyrrolo[2,3,4-kl]acridines 3.

| Entry | Product | R1            | R2            | Time (min) | Isolated Yield (%) |
|-------|---------|---------------|---------------|------------|--------------------|
| 1     | 3a      | H             | 4-t-BuC6H4    | 12         | 91                 |
| 2     | 3b      | H             | 3,5-(CH3)2C6H3 | 12         | 92                 |
| 3     | 3c      | H             | 2-CH3CH2C6H4  | 12         | 92                 |
| 4     | 3d      | H             | 3-Cl-4-FC6H4  | 15         | 89                 |
| 5     | 3e      | 5-Cl          | 4-CH3OC6H4    | 12         | 90                 |
| 6     | 3f      | 5-Cl          | 4-t-BuC6H4    | 12         | 91                 |
| 7     | 3g      | 5-Cl          | 3,5-(CH3)2C6H3 | 12         | 92                 |
| 8     | 3h      | 5-Cl          | 3-Cl-4-FC6H4  | 15         | 90                 |
| 9     | 3i      | 5-Cl          | 2-CH3CH2C6H4  | 12         | 93                 |
| 10    | 3j      | 5-Cl          | n-C6H6        | 15         | 89                 |
| 11    | 3k      | 5-F           | 4-CH3C6H4     | 12         | 92                 |
| 12    | 3l      | 5-F           | 4-ClC6H4      | 12         | 91                 |
| 13    | 3m      | 5-F           | 2,4-(CH3)2C6H3 | 12         | 91                 |
| 14    | 3n      | 5-F           | 3-Cl-4-FC6H4  | 15         | 90                 |
| 15    | 3o      | 5-F           | 4-t-BuC6H4    | 12         | 92                 |
| 16    | 3p      | 5-F           | 2-CH3CH2C6H4  | 12         | 92                 |
| 17    | 3q      | 5-Br          | 4-ClC6H4      | 12         | 93                 |
| 18    | 3r      | 5-Br          | 3-Cl-4-FC6H3  | 15         | 90                 |
| 19    | 3s      | 5-Br          | 4-BrC6H4      | 12         | 90                 |
| 20    | 3t      | 5-Br          | 3,5-(CH3)2C6H3 | 12         | 91                 |
| 21    | 3u      | 5-Br          | n-C6H6        | 15         | 92                 |

To expand the scope of the present method, N-substituted 3-aminocyclohex-2-enone, N-substituted 3-amino-5-phenylcyclohex-2-enones or N-substituted 3-amino-5-methylcyclohex-2-enones (4) were examined to replace the N-substituted 3-amino-5,5-dimethylcyclohex-2-enones (2), to our surprise, under the above optimized conditions, the desired 4,5-dihydropyrrolo[2,3,4-kl]acridine products 3 were not obtained. In the corresponding 1H-NMR spectra, the methylene group signals could not be detected, however a new aromatic proton could be detected easily. This result indicated that the corresponding oxidation products, the pyrrolo[2,3,4-kl]acridine derivatives 5 were produced (Table 3).
The reason is that when there is no substituent or only one substituent (phenyl or methyl) on the C₅ position of N-substituted 3-aminocyclohex-2-enone, the 4,5-dihydropyrrolo[2,3,4-kl]acridine derivatives would be oxidized by oxygen in the air to give pyrrolo[2,3,4-kl]acridine derivatives. The reaction pathways could therefore be controlled by varying the enamines with different substitution patterns to give a series of novel 4,5-dihydropyrrolo[2,3,4-kl]acridin-1-ones 3 and pyrrolo[2,3,4-kl]acridin-1-ones 5 selectively.

**Table 3.** Synthesis of pyrrolo[2,3,4-kl]acridine derivatives 5.

| Entry | Product | R₁ | R₂ | R₃ | Time (min) | Isolated Yield (%) |
|-------|---------|----|----|----|------------|-------------------|
| 1     | 5a      | 5-F | 4-ClC₆H₄ | H  | 15         | 87                |
| 2     | 5b      | 5-F | 2,4-Cl₂C₆H₃ | H  | 15         | 88                |
| 3     | 5c      | 5-F | C₆H₅     | H  | 15         | 87                |
| 4     | 5d      | 5-Cl| 4-BrC₆H₄ | H  | 15         | 88                |
| 5     | 5e      | 5-F | 4-t-BuC₆H₄ | H  | 15         | 86                |
| 6     | 5f      | 5-F | 4-ClC₆H₄ | Ph | 15         | 87                |
| 7     | 5g      | 5-F | 3-Cl-4-FC₆H₃ | Ph | 15         | 84                |
| 8     | 5h      | H   | C₆H₅     | Ph | 15         | 88                |
| 9     | 5i      | 5-F | 2,4-(CH₃)₂C₆H₃ | Ph | 15         | 85                |
| 10    | 5j      | H   | 4-BrC₆H₄ | Ph | 15         | 87                |
| 11    | 5k      | 5-Cl| 4-t-BuC₆H₄ | Ph | 15         | 85                |
| 12    | 5l      | 5-F | C₆H₅     | Ph | 15         | 84                |
| 13    | 5m      | 5-Br| 4-CH₂C₆H₄ | Ph | 15         | 85                |
| 14    | 5n      | 5-Br| 4-OCH₃C₆H₄ | CH₃| 15         | 85                |

The structures of the products 3 and 5 were identified from their IR, ¹H-NMR, and HRMS spectra. The structure of compound 3k was further confirmed by X-ray analysis (Figure 1).

**Figure 1.** Molecular structure of compound 3k.
3. Experimental

3.1. General

All reagents were purchased from commercial suppliers and used without further purification. Melting points are uncorrected. IR spectra were recorded on Varian F-1000 spectrometer in KBr with absorptions in cm\(^{-1}\). \(^1\)H-NMR (300 MHz or 400 MHz) spectra were recorded on a Varian Inova-300 MHz and Varian Inova-400 MHz (Palo Alto, CA, USA) in DMSO-\(d_6\) or CDCl\(_3\) solution. \(J\) values are in Hertz. Chemical shifts are expressed in parts per million downfield from internal standard TMS. High-resolution mass spectra (HRMS) for all the compounds were determined on Bruker MicrOToF-QII mass spectrometer with ESI resource (Billerica, MA, USA). X-ray crystallographic analysis was performed with a Rigaku Mercury CCD/AFC diffractometer (Tokyo, Japan). Microwave irradiation was carried out with an Initiator EXP Microwave Synthesizer from Biotage (Uppsala, Sweden). The reaction temperature was measured by an infrared detector during microwave heating.

3.2. General Procedure for the Synthesis of Compounds 3 and 5

Isatin (1, 1.0 mmol) was introduced in a 10-mL Initiator reaction vial, and enaminone 2 or 4 (1.0 mmol) and 0.02 g of silica sulfuric acid as well as ethanol (3 mL) were then successively added. Subsequently, the reaction vial was closed and prestirred for 10 s. The mixture was irradiated (time, 12 or 15 min; temperature, 110 °C; absorption level, high; fixed hold time) until TLC (petroleum ether/ethyl acetate 3:1) revealed that conversion of the starting material 1 was complete. The reaction mixture was then cooled to room temperature and concentrated. The solid was collected by Büchner filtration and purified by flash column chromatography (silica gel, mixture of petroleum ether/ethyl acetate, 3:1, v/v) to afford the desired products 3 or 5.

2-(4-tert-Butylphenyl)-4,5-dihydro-4,4-dimethylpyrrolo[2,3,4-kl]acridin-1(2H)-one (3a). M.p. 168–170 °C; IR (KBr, cm\(^{-1}\)) 2930, 1690, 1448, 1332, 1075, 959, 891, 831, 700; \(^1\)H-NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) (ppm) 1.28 (s, 6H, 2 × CH\(_3\)), 1.34 (s, 9H, (CH\(_3\))\(_3\)), 3.33 (s, 2H, CH\(_2\)), 5.80 (s, 1H, CH), 7.44 (d, \(J = 8.4\) Hz, 2H, ArH), 7.59 (d, \(J = 8.4\) Hz, 2H, ArH), 7.77 (t, \(J = 7.6\) Hz, 1H, ArH), 7.84–7.88 (m, 1H, ArH), 8.16 (d, \(J = 8.8\) Hz, 1H, ArH), 8.57 (d, \(J = 8.0\) Hz, 1H, ArH). HRMS (ESI): \(m/z\) calcd. for C\(_{26}\)H\(_{27}\)N\(_2\)O\([\text{M+H}]^+\), 383.2123; found, 383.2103.

4,5-Dihydro-4,4-dimethyl-2-(3,5-dimethylphenyl)pyrrolo[2,3,4-kl]acridin-1(2H)-one (3b). M.p. 205–207 °C; IR (KBr, cm\(^{-1}\)) 3064, 1717, 1634, 1499, 1386, 1327, 1257, 1186, 1092, 1018, 777; \(^1\)H-NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) (ppm) 1.20 (s, 6H, 2 × CH\(_3\)), 2.30 (s, 6H, 2 × CH\(_3\)), 3.07 (s, 2H, CH\(_2\)), 5.64 (s, 1H, CH), 7.02–7.04 (m, 3H, ArH), 7.64 (t, \(J = 7.2\) Hz, 1H, ArH), 7.72 (t, \(J = 7.6\) Hz, 1H, ArH), 8.04 (d, \(J = 8.0\) Hz, 1H, ArH), 8.46 (d, \(J = 7.6\) Hz, 1H, ArH). HRMS (ESI): \(m/z\) calcd. for C\(_{24}\)H\(_{23}\)N\(_2\)O\([\text{M+H}]^+\), 355.1810; found, 355.1811.

2-(2-Ethylphenyl)-4,5-dihydro-4,4-dimethylpyrrolo[2,3,4-kl]acridin-1(2H)-one (3c). M.p. 196–198 °C; IR (KBr, cm\(^{-1}\)) 2957, 1708, 1646, 1500, 1348, 1146, 1083, 1016, 896, 830, 738; \(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta\) (ppm) 1.39–1.40 (m, 9H, 3 × CH\(_3\)), 2.39–2.43 (m, 2H, CH\(_3\)), 3.32 (s, 2H, CH\(_2\)), 5.82 (s, 1H, CH), 7.33–7.39 (m, 2H, ArH), 7.59–7.60 (m, 1H, ArH), 7.73–7.82 (m, 3H, ArH), 8.27–8.30 (m, 1H, CH), 8.57 (d, \(J = 8.0\) Hz, 1H, ArH), 8.46 (d, \(J = 7.6\) Hz, 1H, ArH). HRMS (ESI): \(m/z\) calcd. for C\(_{30}\)H\(_{28}\)N\(_2\)O\([\text{M+H}]^+\), 429.2132; found, 429.2132.
ArH), 8.72–8.74 (m, 1H, ArH). HRMS (ESI): m/z calcd. for C_{24}H_{23}N_{2}O [M+H]^+, 355.1810; found, 355.1823.

2-(3-Chloro-4-fluorophenyl)-4,5-dihydro-4,4-dimethylpyrrolo[2,3,4-kl]acridin-1(2H)-one (3d). M.p. 168–169 °C; IR (KBr, cm\(^{-1}\)) 2958, 1710, 1462, 1356, 1171, 1100, 880, 755; \(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta\) (ppm) 1.34 (s, 6H, 2 × CH\(_3\)), 3.26 (s, 2H, CH\(_2\)), 5.60 (s, 1H, CH), 7.31–7.38 (m, 2H, ArH), 7.56 (s, 1H, ArH), 7.69–7.78 (m, 2H, ArH), 8.20–8.21 (m, 1H, ArH), 8.69–8.70 (m, 1H, ArH). HRMS (ESI): m/z calcd. for C_{24}H_{23}N_{2}O [M+H]^+, 355.1810; found, 355.1823.

9-Chloro-4,5-dihydro-2-(4-methoxyphenyl)-4,4-dimethylpyrrolo[2,3,4-kl]acridin-1(2H)-one (3e). M.p. 162–164 °C; IR (KBr, cm\(^{-1}\)) 2954, 1704, 1494, 1342, 1121, 1009, 819; \(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta\) (ppm) 1.32 (s, 6H, 2 × CH\(_3\)), 3.18 (s, 3H, OCH\(_3\)), 3.87 (s, 2H, CH\(_2\)), 5.59 (s, 1H, CH), 7.04 (d, \(J = 6.6\) Hz, 2H, ArH), 7.38 (d, \(J = 6.6\) Hz, 2H, ArH), 7.65 (d, \(J = 7.2\) Hz, 1H, ArH), 8.05 (d, \(J = 8.7\) Hz, 1H, ArH), 8.66 (s, 1H, ArH). HRMS (ESI): m/z calcd. for C_{23}H_{20}ClN_{2}O_{2} [M+H]^+, 391.1213; found, 391.1194.

2-(4-Tert-butylphenyl)-9-chloro-4,5-dihydro-4,4-dimethylpyrrolo[2,3,4-kl]acridin-1(2H)-one (3f). M.p. 182–184 °C; IR (KBr, cm\(^{-1}\)) 2947, 1575, 1485, 1392, 1319, 1253, 1077, 989, 833, 717; \(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta\) (ppm) 1.33 (s, 6H, 2 × CH\(_3\)), 1.38 (s, 9H, (CH\(_3\))\(_3\)), 3.19 (s, 2H, CH\(_2\)), 5.68 (s, 1H, CH), 7.42 (s, 2H, ArH), 7.56–7.57 (m, 2H, ArH), 7.66–7.68 (m, 1H, ArH), 8.08–8.09 (m, 1H, ArH), 8.69 (s, 1H, ArH). HRMS (ESI): m/z calcd. for C_{26}H_{26}ClN_{2}O [M+H]^+, 417.1734; found, 417.1768.

9-Chloro-4,5-dihydro-4,4-dimethyl-2-(3,5-dimethylphenyl)pyrrolo[2,3,4-kl]acridin-1(2H)-one (3g). M.p. 178–180 °C; IR (KBr, cm\(^{-1}\)) 2928, 1705, 1636, 1521, 1474, 1396, 1254, 1176, 1109, 1035, 803; \(^1\)H-NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) (ppm) 1.11 (s, 6H, 2 × CH\(_3\)), 2.21 (s, 6H, 2 × CH\(_3\)), 2.97 (s, 2H, CH\(_2\)), 5.61 (s, 1H, CH), 6.94 (s, 3H, ArH), 7.61–7.65 (m, 1H, ArH), 7.91 (d, \(J = 8.8\) Hz, 1H, ArH), 8.23 (s, 1H, ArH). HRMS (ESI): m/z calcd. for C_{24}H_{22}ClN_{2}O [M+H]^+, 389.1421; found, 389.1405.

9-Chloro-2-(3-chloro-4-fluorophenyl)-4,5-dihydro-4,4-dimethylpyrrolo[2,3,4-kl]acridin-1(2H)-one (3h). M.p. 164–166 °C; IR (KBr, cm\(^{-1}\)) 2944, 1703, 1638, 1516, 1457, 1351, 1209, 1087, 910, 879, 804; \(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta\) (ppm) 1.14–1.16 (m, 3H, CH\(_3\)), 1.31 (s, 6H, 2 × CH\(_3\)), 1.35 (s, 6H, 2 × CH\(_3\)), 2.56 (s, 2H, CH\(_2\)), 3.20 (s, 2H, CH\(_2\)), 5.29 (s, 1H, CH), 7.27 (s, 1H, ArH), 7.36 (s, 1H, ArH), 7.45 (s, 2H, ArH), 7.67 (d, \(J = 8.1\) Hz, 1H, ArH), 8.09 (d, \(J = 6.9\) Hz, 1H, ArH), 8.66 (s, 1H, ArH). HRMS (ESI): m/z calcd. for C_{24}H_{22}Cl_{2}FN_{2}O [M+H]^+, 413.0624; found, 413.0608.

2-Butyl-9-chloro-4,5-dihydro-4,4-dimethylpyrrolo[2,3,4-kl]acridin-1(2H)-one (3j). M.p. 148–149 °C; IR (KBr, cm\(^{-1}\)) 2950, 1706, 1500, 1346, 1240, 1091, 956, 890, 824, 697; \(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta\) (ppm) 0.92–0.94 (m, 3H, CH\(_3\)), 1.29–1.36 (m, 8H, CH\(_2\) + 2 × CH\(_3\)), 1.66–1.67 (m, 2H, CH\(_2\)), 3.09–3.10 (m, 2H, CH\(_2\)), 3.73–3.74 (m, 2H, CH\(_2\)), 5.51 (s, 1H, CH), 7.57–7.58 (m, 1H, ArH), 7.96–7.98 (m, 1H, ArH).
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ArH), 8.56 (s, 1H, ArH). HRMS (ESI): m/z calcld. for C20H22ClN2O [M+H]+, 341.1421; found, 341.1412.

2-(4-tert-Butylphenyl)-9-fluoro-4,5-dihydro-4,4-dimethylpyrrolo[2,3,4-kl]acridin-1(2H)-one (3k).
M.p. 168–170 °C; IR (KBr, cm⁻¹) 3079, 1711, 1635, 1504, 1403, 1256, 1119, 1063, 775, 707; ¹H-NMR (400 MHz, DMSO-d₆): δ (ppm) 1.24 (s, 6H, 2 × CH₃), 2.38 (s, 3H, CH₃), 3.08 (s, 2H, CH₂), 5.70 (s, 1H, CH), 7.31–7.36 (m, 4H, ArH), 7.60 (s, 1H, ArH), 8.00–8.09 (m, 2H, ArH). HRMS (ESI): m/z calcld. for C22H24F2N2O [M+H]+, 379.1013; found, 379.1005.

2-(4-Chlorophenyl)-9-fluoro-4,5-dihydro-4,4-dimethylpyrrolo[2,3,4-kl]acridin-1(2H)-one (3l).
M.p. 192–195 °C; IR (KBr, cm⁻¹) 2957, 1703, 1508, 1360, 1223, 1110, 825, 699; ¹H-NMR (300 MHz, CDCl₃): δ (ppm) 1.32 (s, 6H, 2 × CH₃), 3.19 (s, 2H, CH₂), 5.63 (s, 1H, CH), 7.44–7.52 (s, 5H, ArH), 8.12–8.16 (m, 1H, ArH), 8.28–8.31 (m, 1H, ArH). HRMS (ESI): m/z calcld. for C22H17ClFN₂O [M+H]+, 380.0913; found, 380.0909.

9-Fluoro-4,5-dihydro-4,4-dimethyl-2-(2,4-dimethylphenyl)pyrrolo[2,3,4-kl]acridin-1(2H)-one (3m).
M.p. 148–150 °C; IR (KBr, cm⁻¹) 2940, 1697, 1602, 1454, 1354, 1251, 1096, 970, 896, 834, 707; ¹H-NMR (300 MHz, CDCl₃): δ (ppm) 1.28 (s, 6H, 2 × CH₃), 2.06 (s, 3H, CH₃), 2.35 (s, 3H, CH₃), 3.17 (s, 2H, CH₂), 5.28 (s, 1H, CH), 7.13 (s, 1H, ArH), 7.24 (s, 2H, ArH), 7.46–7.48 (m, 1H, ArH), 7.97 (s, 1H, ArH), 8.07 (s, 1H, ArH). HRMS (ESI): m/z calcld. for C24H22FN₂O [M+H]+, 373.1716; found, 373.1699.

2-(3-Chloro-4-fluorophenyl)-9-fluoro-4,5-dihydro-4,4-dimethylpyrrolo[2,3,4-kl]acridin-1(2H)-one (3n).
M.p. 204–206 °C; IR (KBr, cm⁻¹) 2950, 1707, 1639, 1493, 1348, 1201, 1086, 1017, 955, 833; ¹H-NMR (400 MHz, DMSO-d₆): δ (ppm) 1.19 (s, 6H, 2 × CH₃), 1.27 (s, 9H, (CH₃)₃), 3.04 (s, 2H, CH₂), 5.70 (s, 1H, CH), 7.36–7.37 (m, 2H, ArH), 7.51–7.59 (m, 3H, ArH), 7.97 (s, 1H, ArH), 8.07 (s, 1H, ArH). HRMS (ESI): m/z calcld. for C24H26F₂N₂O [M+H]+, 401.2029; found, 401.2034.
7.80 (s, 1H, ArH), 7.97 (s, 1H, ArH), 8.81 (s, 1H, ArH). HRMS (ESI): m/z calcd. for C_{22}H_{17}BrClN_{2}O [M+H]^+; 439.0213; found, 439.0197.

9-Bromo-2-(3-chloro-4-fluorophenyl)-4,5-dihydro-4,4-dimethylpyrrolo[2,3,4-kl]acridin-1(2H)-one (3r). M.p. 168–170 °C; IR (KBr, cm\(^{-1}\)) 2950, 1704, 1588, 1495, 1439, 1347, 1084, 822, 702; \(^1\)H-NMR (300 MHz, CDCl\(_3\)): δ (ppm) 1.33 (s, 6H, 2 × CH\(_3\)), 3.18 (s, 2H, CH\(_2\)), 5.63 (s, 1H, CH), 7.30–7.36 (m, 2H, ArH), 7.56 (s, 1H, ArH), 7.79 (d, J = 6.6 Hz, 1H, ArH), 7.98 (d, J = 8.4 Hz, 1H, ArH), 8.77 (s, 1H, CH). HRMS (ESI): m/z calcd. for C_{22}H_{16}BrClN_{2}O [M+H]^+; 457.0119; found, 457.0103.

9-Bromo-2-(4-bromophenyl)-4,5-dihydro-4,4-dimethylpyrrolo[2,3,4-kl]acridin-1(2H)-one (3s). M.p. 182–184 °C; IR (KBr, cm\(^{-1}\)) 2955, 1709, 1590, 1459, 1343, 1159, 1013, 889, 832, 766, 705; \(^1\)H-NMR (300 MHz, CDCl\(_3\)): δ (ppm) 1.32 (s, 6H, 2 × CH\(_3\)), 3.18 (s, 2H, CH\(_2\)), 5.64 (s, 1H, CH), 7.37–7.39 (m, 2H, ArH), 7.65 (s, 2H, ArH), 7.79–7.82 (m, 1H, ArH), 7.99 (d, J = 6.9 Hz, 1H, ArH), 8.82 (s, 1H, CH). HRMS (ESI): m/z calcd. for C_{22}H_{17}Br_{2}N_{2}O [M+H]^+; 482.9708; found, 482.9693.

9-Bromo-4,5-dihydro-4,4-dimethyl-2-(3,5-dimethylphenyl)pyrrolo[2,3,4-kl]acridin-1(2H)-one (3t). M.p. 164–166 °C; IR (KBr, cm\(^{-1}\)) 2958, 1915, 1612, 1550, 1445, 1318, 1229, 1101, 984, 823, 715; \(^1\)H-NMR (300 MHz, CDCl\(_3\)): δ (ppm) 1.31 (s, 6H, 2 × CH\(_3\)), 2.39 (s, 6H, 2 × CH\(_3\)), 3.16 (s, 2H, CH\(_2\)), 5.63 (s, 1H, CH), 7.03–7.07 (m, 3H, ArH), 7.22 (d, J = 6.0 Hz, 1H, ArH), 7.96–7.98 (m, 1H, ArH), 8.83 (s, 1H, CH). HRMS (ESI): m/z calcd. for C_{24}H_{22}BrN_{2}O [M+H]^+; 433.0916; found, 433.0906.

9-Bromo-2-butyl-4,5-dihydro-4,4-dimethylpyrrolo[2,3,4-kl]acridin-1(2H)-one (3u). M.p. 156–158 °C; IR (KBr, cm\(^{-1}\)) 2938, 1699, 1510, 1450, 1356, 1245, 1126, 1028, 831, 789; \(^1\)H-NMR (300 MHz, CDCl\(_3\)): δ (ppm) 0.95 (s, 3H, CH\(_3\)), 1.32–1.38 (m, 8H, CH\(_2\) + 2 × CH\(_3\)), 1.69–1.70 (m, 2H, CH\(_2\)), 3.77 (s, 2H, CH\(_2\)), 5.54 (s, 1H, CH), 7.74 (d, J = 7.2 Hz, 1H, ArH), 7.94 (d, J = 8.7 Hz, 1H, ArH), 8.78 (s, 1H, ArH). HRMS (ESI): m/z calcd. for C_{20}H_{22}BrN_{2}O [M+H]^+; 385.0917; found, 385.0917.

2-(4-Chlorophenyl)-9-fluoropyrrolo[2,3,4-kl]acridin-1(2H)-one (5a). M.p. 237–238 °C; IR (KBr, cm\(^{-1}\)) 3022, 1716, 1638, 1185, 1074, 874; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): δ (ppm) 7.02–7.04 (m, 1H, ArH), 7.56–7.59 (m, 4H, ArH), 7.69–7.73 (m, 2H, ArH), 7.90 (d, J = 9.2 Hz 1H, ArH), 8.44–8.50 (m, 2H, ArH). HRMS (ESI): m/z calcd. for C_{20}H_{16}ClFN_{2}NaO, 371.0363; [M+Na]^+; found, 371.0345.

2-(2,4-Dichlorophenyl)-9-fluoropyrrolo[2,3,4-kl]acridin-1(2H)-one (5b). M.p. 248–250 °C; IR (KBr, cm\(^{-1}\)) 3050, 1723, 1639, 1182, 1089, 785; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): δ (ppm) 6.66 (d, J = 6.8 Hz 1H, ArH), 7.43–7.45 (m, 1H, ArH), 7.58 (d, J = 8.0 Hz, 2H, ArH), 7.69–7.73 (m, 2H, ArH), 7.92 (d, J = 8.8 Hz 1H, ArH), 8.49–8.53 (m, 2H, ArH). HRMS (ESI): m/z calcd. for C_{20}H_{9}Cl_{2}FN_{2}NaO, 404.9974, [M+Na]^+; found, 404.9989.

9-Fluoro-2-phenylpyrrolo[2,3,4-kl]acridin-1(2H)-one (5c). M.p. 228–230 °C; IR (KBr, cm\(^{-1}\)) 2978, 1716, 1673, 1262, 1185, 1074, 874; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): δ (ppm) 7.03 (d, J = 6.8 Hz 1H, ArH), 7.46–7.47 (m, 1H, ArH), 7.60–7.76 (m, 6H, ArH), 7.87 (d, J = 8.8 Hz 1H, ArH), 8.43–8.50 (m, 2H, ArH). HRMS (ESI): m/z calcd. for C_{20}H_{11}FN_{2}NaO, 337.0753, [M+Na]^+; found, 337.0769.
2-(4-Bromophenyl)-9-chloropyrrolo[2,3,4-kl]acridin-1(2H)-one (5d). M.p. 218–220 °C; IR (KBr, cm⁻¹) 2978, 1706, 1632, 1503, 1118 1096, 854; ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 6.70–6.71 (m, 1H, ArH), 7.48–7.59 (m, 3H, ArH), 7.64–7.71 (m, 3H, ArH), 7.87–7.89 (m, 1H, ArH), 8.43–8.49 (m, 2H, ArH). HRMS (ESI): m/z calcd. for C₂₀H₁₀BrClN₂NaO, 430.5963, [M+Na]+; found, 430.5978.

2-(4-tert-Butylphenyl)-9-fluoropyrrolo[2,3,4-kl]acridin-1(2H)-one (5e). M.p. 162–164 °C; IR (KBr, cm⁻¹) 2951, 1710, 1628, 1512, 1353, 1205, 1096, 830, 718; ¹H-NMR (300 MHz, CDCl₃): δ (ppm) 1.42 (s, 9H, C(CH₃)₃), 7.04–7.06 (m, 1H, ArH), 7.57–7.71 (m, 6H, ArH), 7.85–7.89 (m, 1H, ArH), 8.44–8.51 (m, 2H, ArH). HRMS (ESI): m/z calcd. for C₂₄H₂₀FN₂O, 370.1481, [M+H]+; found, 371.1537.

2-(4-Chlorophenyl)-9-fluoro-4-phenylpyrrolo[2,3,4-kl]acridin-1(2H)-one (5f). M.p. 238–240 °C; IR (KBr, cm⁻¹) 2930, 2354, 1716, 1639, 1499, 1087, 812; ¹H-NMR (300 MHz, CDCl₃): δ (ppm) 7.46–7.69 (m, 11H, ArH), 8.04–8.05 (m, 1H, ArH), 8.41–8.42 (m, 2H, ArH). HRMS (ESI): m/z calcd. for C₂₆H₁₅ClFN₂O, 425.0857, [M+H]+; found, 425.0846.

2-(3-Chloro-4-fluorophenyl)-9-fluoro-4-phenylpyrrolo[2,3,4-kl]acridin-1(2H)-one (5g). M.p. 230–232 °C; IR (KBr, cm⁻¹) 3069, 2926, 2354, 1716, 1640, 1384, 1092, 812; ¹H-NMR (300 MHz, CDCl₃): δ (ppm) 7.29–7.54 (m, 6H, ArH), 7.70–7.76 (m, 4H, ArH), 8.01–8.02 (m, 1H, ArH), 8.42–8.45 (m, 2H, ArH). HRMS (ESI): m/z calcd. for C₂₆H₁₄ClF₂N₂O, 443.0763 [M+H]+; found, 443.0770.

2,4-Diphenylpyrrolo[2,3,4-kl]acridin-1(2H)-one (5h). M.p. 220–221 °C; IR (KBr, cm⁻¹) 2921, 1718, 1637, 1496, 1103, 1008, 761; ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.27 (s, 1H, ArH), 7.45–7.53 (m, 4H, ArH), 7.60–7.73 (m, 6H, ArH), 7.80 (t, J = 8.0 Hz, 1H, ArH), 7.93 (t, J = 8.4 Hz, 1H, ArH), 8.06 (s, 1H, ArH), 8.42 (d, J = 8.8 Hz, 1H, ArH), 8.89 (d, J = 8.0 Hz, 1H, ArH). HRMS (ESI): m/z calcd. for C₂₆H₁₆N₂NaO, 395.1160 [M+Na]+; found, 395.1182.

9-Fluoro-2-(2,4-dimethylphenyl)-4-phenylpyrrolo[2,3,4-kl]acridin-1(2H)-one (5i). M.p. 188–190 °C; IR (KBr, cm⁻¹) 2990, 1705, 1633, 1131, 1066, 854; ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 2.08 (s, 3H, CH₃), 2.26 (s, 3H, CH₃), 6.72–6.73 (m, 1H, ArH), 7.03–7.16 (m, 3H, ArH), 7.22–7.29 (m, 3H, ArH), 7.47–7.49 (m, 3H, ArH), 7.82–7.84 (m, 1H, ArH), 8.22–8.27 (m, 2H, ArH). HRMS (ESI): m/z calcd. for C₂₈H₂₀FN₂O, 419.1560, [M+H]+; found, 419.1559.

2-(4-Bromophenyl)-4-phenylpyrrolo[2,3,4-kl]acridin-1(2H)-one (5j). M.p. 234–235 °C; IR (KBr, cm⁻¹) ν2987, 1703, 1636, 1501, 1253, 1181, 1085, 832. ¹H-NMR (CDCl₃-d₁, 400 MHz) δ : 7.22 (s, 1H, ArH), 7.40–7.56 (m, 5H, ArH), 7.69–7.79 (m, 5H, ArH), 7.91 (t, J = 7.6 Hz, 1H, ArH), 8.05 (s, 1H, ArH), 8.40 (d, J = 8.8 Hz, 1H, ArH), 8.83 (d, J = 8.4 Hz, 1H, ArH). HRMS (ESI): m/z calcd. for C₂₆H₁₆BrN₂O, 451.0446, [M+H]+; found, 451.0409.

2-(4-tert-Butylphenyl)-9-chloro-4-phenylpyrrolo[2,3,4-kl]acridin-1(2H)-one (5k). M.p. 222–223 °C; IR (KBr, cm⁻¹) 2922, 1719, 1634, 1383, 1171, 1077, 822; ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 1.42 (s, 9H, (CH₃)₃), 7.19–7.22 (m, 1H, ArH), 7.42–7.68 (m, 9H, ArH), 7.75–7.80 (m, 1H, ArH), 7.92–7.96 (m, 1H, ArH), 8.27–8.31 (m, 1H, ArH), 8.73–8.78 (m, 1H, ArH) HRMS (ESI): m/z calcd. for C₃₀H₂₂ClN₂O, 463.1577, [M+H]+; found, 463.1570.
9-Fluoro-2,4-diphenylpyrrolo[2,3,4-kl]acridin-1(2H)-one (5l). M.p. 218–219 °C; IR (KBr, cm\(^{-1}\)) 2957, 1705, 1633, 1096, 854; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 7.43–7.51 (m, 4H, ArH), 7.59–7.70 (m, 8H, ArH), 8.01–8.02 (m, 1H, ArH), 8.41–8.43 (m, 2H, ArH). HRMS (ESI): \(m/z\) calcd. for C\(_{26}\)H\(_{16}\)FN\(_2\)O, 391.1247, [M+H]\(^+\); found, 391.1229.

9-Bromo-4-phenyl-2-p-tolylpyrrolo[2,3,4-kl]acridin-1(2H)-one (5m). M.p. 220–222 °C; IR (KBr, cm\(^{-1}\)) 2921, 1706, 1635, 1384, 1129, 1092, 820; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 2.45 (s, 3H, CH\(_3\)), 7.17 (s, 1H, ArH), 7.38–7.50 (m, 7H, ArH), 7.65 (d, \(J = 7.6\) Hz, 2H, ArH), 7.89–7.95 (m, 2H, ArH), 8.21 (d, \(J = 9.2\) Hz, 1H, ArH), 8.98 (s, 1H, ArH). HRMS (ESI): \(m/z\) calcd. for C\(_{27}\)H\(_{17}\)BrN\(_2\)NaO, 487.0422, [M+H]\(^+\); found, 487.0403.

9-Bromo-2-(4-methoxyphenyl)-4-methylpyrrolo[2,3,4-kl]acridin-1(2H)-one (5n). M.p. 216–218 °C; IR (KBr, cm\(^{-1}\)) 2916, 1718, 1637, 1516, 1384, 1124, 1080, 849; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 2.50 (s, 3H, CH\(_3\)), 2.60 (s, 3H, OCH\(_3\)), 6.82 (s, 1H, ArH), 7.41–7.60 (m, 5H, ArH), 7.93–7.96 (m, 1H, ArH), 8.24–8.26 (m, 1H, ArH), 9.03–9.04 (m, 1H, ArH). HRMS (ESI): \(m/z\) calcd. for C\(_{22}\)H\(_{15}\)BrN\(_2\)NaO\(_2\), 441.0215, [M+Na]\(^+\); found, 441.0218.

4. Conclusions

In conclusion, we have developed a procedure for the simple synthesis of a variety of potential biologically active pyrrolo[2,3,4-kl]acridines based on a novel domino reaction. Using this method, a library of molecularly diverse pyrrolo[2,3,4-kl]acridine derivatives was rapidly assembled (12–15 min) with excellent yields (84%–93%) by using readily available and inexpensive substrates under microwave irradiation.

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References

1. Desbois, N.; Gardette, M.; Papon, J.; Labarre, P.; Maisonal, A.; Auzeloux, P.; Lartigue, C.; Bouchon, B.; Debiton, E.; Blache, Y.; et al. Design, synthesis and preliminary biological evaluation of acridine compounds as potential agents for a combined targeted chemo-radionuclide therapy approach to melanoma. *Bioorg. Med. Chem.* **2008**, *16*, 7671–7690.

2. Oppegard, L.M.; Ougolkov, A.V.; Luchini, D.N.; Schoon, R.A.; Goodell, J.R.; Kaur, H.; Billadeau, D.D.; Ferguson, D.M.; Hiasa, H. Novel acridine-based compounds that exhibit an anti-pancreatic cancer activity are catalytic inhibitors of human topoisomerase. *Eur. J. Pharmacol.* **2009**, *602*, 223–229.
3. Mccapra, F.; Acheson, R.M. *The Chemistry of Heterocyclic Compounds: Acridines*; John Wiley & Sons: Hoboken, NJ, USA, 1973; pp. 615–630.

4. Goodell, J.R.; Ougolkov, A.V.; Hiasa, H.; Kaur, H.; Remmel, R.; Billadeau, D.D.; Ferguson, D.M. Acridine-based agents with topoisomerase II activity inhibit pancreatic cancer cell proliferation and induce apoptosis. *J. Med. Chem.* **2008**, *51*, 179–182.

5. Kapuriya, N.; Kapuriya, K.; Zhang, X.; Chou, T.C.; Kakadiya, R.; Wu, Y.T.; Tsai, T.H.; Chen, Y.T.; Lee, T.C.; Shah, A.; et al. Synthesis and biological activity of potent antitumor agents, aniline nitrogen mustards linked to 9-anilinoacridines via a urea linkage. *Bioorg. Med. Chem.* **2008**, *16*, 5413–5423.

6. Belmont, P.; Dorange, I. Acridine/acridone: A simple scaffold with a wide range of application in oncology. *Expert Opin. Ther. Pat.* **2008**, *18*, 1211–1224.

7. Taraporewala, I.B. Thiazolo[5,4-b]acridines and thiazolo[4,5-b]acridines: Probable pharmacophores of antiviral and anti-tumor marine alkaloids. *Tetrahedron Lett.* **1991**, *32*, 39–42.

8. Kavitha, H.P. Synthesis and antimicrobial activity of 1-(9'-Acridinyl)-5-(4-substituted phenyl)tetrazoles. *Asian J. Chem.* **2004**, *16*, 1191–1193.

9. Fattorusso, C.; Campiani, G.; Kukreja, G.; Persico, M.; Butini, S.; Romano, M.P.; Altarelli, M.; Ros, S.; Brindisi, M.; Savini, L.; et al. Design, synthesis and structure-activity relationship studies of 4-quinolinyl- and 9-acridinylhydroazones as potent antimalarial agents. *J. Med. Chem.* **2008**, *51*, 1333–1343.

10. Giorgio, C.D.; Shimi, K.; Boyer, G.; Delmas, F.; Galy, J.P. Synthesis and antileishmanial activity of 6-mono-substituted and 3,6-di-substituted acridines obtained by acylation of proflavine. *Eur. J. Med. Chem.* **2007**, *42*, 1277–1284.

11. Patel, N.A.; Surti, S.C.; Patel, R.G.; Patel, M.P. Synthesis, characterization, and biological activity of some new benzoic acid and thiazoloacridine derivatives. *Phosphorus Sulfur Silicon Relat. Elem.* **2008**, *183*, 2191–2203.

12. Chauhan, P.M.S.; Srivastava, S.K. Present trends and future strategy in chemotherapy of malaria. *Curr. Med. Chem.* **2001**, *8*, 1535–1542.

13. Lee, Y.; Hyun, S.; Kim, H.J.; Yu, J. Amphiphilic helical peptides containing two acridine moieties display picomolar affinity toward HIV-1 RRE and TAR. *Angew. Chem. Int. Ed.* **2008**, *47*, 134–137.

14. Inman, W.D.; O’Neill-Johnson, M.; Crews, P. Novel marine sponge alkaloids. 1. Plakinidine A and B, anthelmintic active alkaloids from a Plakortis sponge. *J. Am. Chem. Soc.* **1990**, *112*, 1–4.

15. West, R.R.; Mayne, C.L.; Ireland, C.M.; Brinen, L.S.; Clardy, J. Plakinidines: Cytotoxic alkaloid pigments from the fijian sponge plakortis sp. *Tetrahedron Lett.* **1990**, *31*, 3271–3274.

16. Gellerman, G.; Rudi, A.; Kashman, Y. The biomimetic synthesis of marine alkaloid related pyrido- and pyrrolo[2,3,4-kl]acridines. *Tetrahedron* **1994**, *50*, 12959–12972.

17. Kitahara, Y.; Mizuno, T.; Kubo, A. Synthetic studies of benzo[b]pyrrolo[4,3,2-de][1,10]phenanthroline. *Tetrahedron* **2004**, *60*, 4283–4288.

18. Wang, H.Y.; Li, L.L.; Lin, W.; Xu, P.; Huang, Z.B.; Shi, D.Q. An efficient synthesis of pyrrolo[2,3,4-kl]acridin-1-one derivatives catalyzed by L-proline. *Org. Lett.* **2012**, *14*, 4598–4601.
19. Jiang B.; Wang, X.; Li, M.Y.; Wu, Q.; Ye, Q.; Xu, H.W.; Tu, S.J. A domino synthetic strategy leading to two-carbon-tethered fused acridine/indole pairs and fused acridine derivatives. *Org. Biomol. Chem.* **2012**, *10*, 8533–8538.

20. Wang, Y.L.; Lu, G.Z.; Wu, L.Q. Silica sulfuric acid as heterogeneous and recoverable catalysts for the synthesis of dithienylmethanes under solvent-free conditions. *Asian J. Chem.* **2011**, *23*, 4221–4222.

21. Landarani-Isfahani, A.; Safari, J.; Ghotbinejad, M.; Gandomi-Ravandi, S.; Moshtael. Silica sulfuric acid (SSA), a novel catalyst for synthesis of some-α-phenylhydrazone-2-ketomethylquinolines. *Org. Chem. An Indian J.* **2009**, *5*, 39–42.

22. Mobinkhaledi, A.; Foroughifar, N.; Khodaei, H. Synthesis of octahydroquinazolinone derivatives using silica sulfuric acid as an efficient catalyst. *Eur. J. Chem.* **2010**, *1*, 291–293.

23. Azizian, J.; Mohammadi, A.A.; Soleimani, E.; Karimi, A.R.; Mohammadizadeh, M.R. A stereoselective three-component reaction: One-pot synthesis of cis-isoquinolonic acids catalyzed by silica sulfuric acid under mild and heterogeneous conditions. *J. Heterocycl. Chem.* **2006**, *43*, 187–190.

24. Ziarani, G.M.; Badiei, A.; Abbasi, A.; Farahani, Z. Cross-aldol condensation of cycloalkanones and aromatic aldehydes in the presence of nanoporous silica-based sulfonic acid (SiO$_2$-Pr-SO$_3$H) under solvent free conditions, *Chin. J. Chem.* **2009**, *27*, 1537–1542.

25. Aoyama, T.; Kubota, S.; Takido, T.; Kodomari, M. Silica sulfuric acid-promoted deacylation of α-bromo-β-diketones. *Chem. Lett.* **2011**, *40*, 484–485.

26. Ghorbani-Choghamarani, A.; Zamani, P. Ammonium bromide as an effective and viable catalyst in the oxidation of sulfides using nitro urea and silica sulfuric acid. *J. Iran. Chem. Soc.* **2011**, *8*, 142–148.

27. Wang, Y.; Yuan, Y.Q.; Guo, S.R. Silica sulfuric acid promotes Aza-Michael addition reactions under solvent-free condition as a heterogeneous and reusable catalyst. *Molecules* **2009**, *14*, 4779–4789.

28. Kiasat, A.R.; Kazemi, F.; Mehrjardi, M.F. Protection of carbonyl groups as 2,4-dinitrophenyldrazone catalyzed by silica sulfuric acid. *Asian J. Chem.* **2006**, *18*, 969–972.

29. Wu, H.; Shen, Y.; Fan, L.Y.; Wan, Y.; Wang, W.X.; Shi, D.Q. Solid silica sulfuric acid (SSA) as a novel and efficient catalyst for acetylation of aldehydes and sugars. *Tetrahedron* **2006**, *62*, 7995–7998.

30. Wu, H.; Lin, W.; Wan, Y.; Xin, H.Q.; Shi, D.Q.; Shi, Y.H.; Yuan, R.; Bo, R.C.; Yin, W. Silica gel-catalyzed one-pot synthesis in water and fluorescence properties studies of 5-amino-2-aryl-3H-chromeno[4,3,2-de][1,8]naphthyridine-4-carbonitriles and 5-amino-2-aryl-3H-quinolino[4,3,2-de][1,6]naphthyridine-4-carbonitriles. *J. Comb. Chem.* **2010**, *12*, 31–34.

*Sample Availability*: Samples of the compounds 3 and 5 are available from the authors.

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