Improved and Practical Procedures for the Preparation of Highly Substituted Pyridines and Pyridazines via Silica-Mediated Aromatisation

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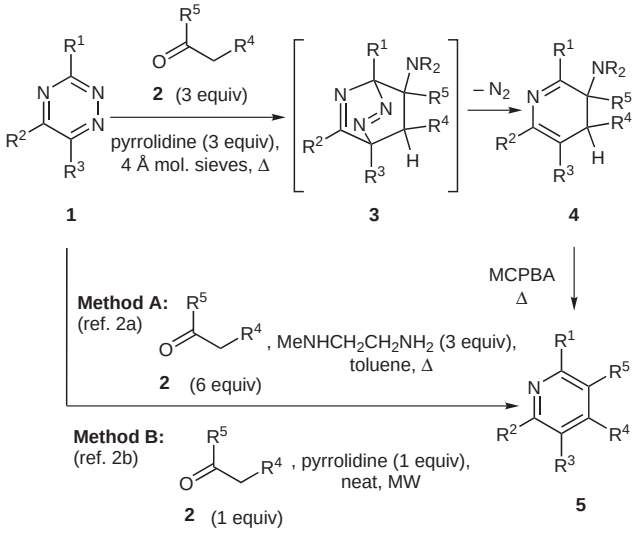
Received 27 April 2007

Abstract: A new and straightforward procedure is described for the preparation of highly substituted pyridines and pyridazines. The method involves a Diels–Alder/retro-Diels–Alder sequence leading to dihydropyridine or related intermediates, which can be aromatized to pyridines and pyridazines by treatment with silica gel. The value of this procedure has been demonstrated with a one-step synthesis of an E-ring-modified steroid.

Key words: Diels–Alder reaction, heterocycles, pyridines, pyridazines, fused-ring systems, silica-mediated aromatization

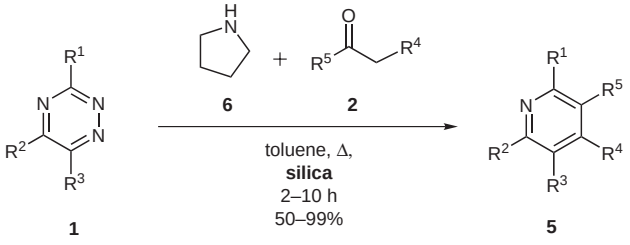
The wide-ranging biological activity associated with many pyridine derivatives, both naturally occurring and synthetic, ensures that improved methods for the preparation of these important heterocyclic systems are of continuing interest.[1] As part of an ongoing research programme to develop efficient and reliable methodologies for the synthesis of heterocyclic and heteroaromatic compounds, we have recently investigated routes to highly substituted pyridine derivatives.[2] Initial studies utilised reactions between polysubstituted 1,2,4-triazines **1**[3] and enamines formed by reaction of ketones **2** with pyrrolidine using Boger's in situ protocol.[4] Under standard thermal conditions, an inverse electron-demand Diels–Alder/retro-Diels–Alder sequence, via intermediate **3**, proceeded smoothly but in situ elimination–aromatisation was not observed and dihydropyridines **4** were isolated in excellent yield (Scheme 1). Such observations concerning the difficulty of aromatising dihydropyridines **4** have been described before and the use of Cope elimination to achieve aromatisation has been reported.[2b,5]

In order to overcome this limitation and to develop one-pot routes to highly substituted pyridines, we went on to design first a novel tethered imine–enamine (TIE) approach (Method A)[2a] and subsequently to develop a solvent-free microwave (MW) procedure (Method B).[2b] The microwave-assisted, solvent-free route proved useful for the conversion of 1,2,4-triazines into a wide range of highly substituted pyridines in good to excellent yield with relatively short reaction times and stoichiometric use of ketone and amine. However, the MW method is limited in terms of scale.



Scheme 1

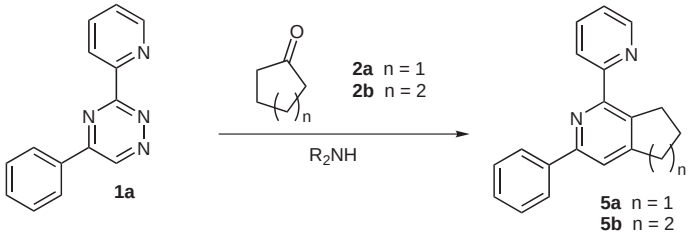
In this communication we describe an improved one-pot procedure for the synthesis of highly substituted pyridines which simply utilises silica gel to facilitate the elimination–aromatisation of dihydropyridines **4** and which can be easily adapted to larger-scale processes (Scheme 2). This improved procedure was discovered when trying to isolate dihydropyridines **4**. It was found that after slow chromatography through a column of silica gel, an appreciable quantity of pyridine **5** was obtained. Following this serendipitous observation, and after optimisation of reaction conditions, an improved thermal approach to the preparation of highly substituted pyridines was developed. The essence of this new route consists of the addition of a small quantity of silica gel (Fluka, flash chromatography silica gel 60, 220–440 mesh) to the reaction mixture, made up of 1,2,4-triazine **1**, 1.5 equivalents of ketone **2**, and pyrrolidine (**6**, Scheme 2).[6]

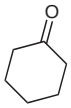


Scheme 2

SYNLETT 2007, No. 14, pp 2217–2221
Advanced online publication: 23.07.2007
DOI: 10.1055/s-2007-984918; Art ID: D18507ST

Table 1 Comparison of the One-Pot Methods for Pyridine Preparation

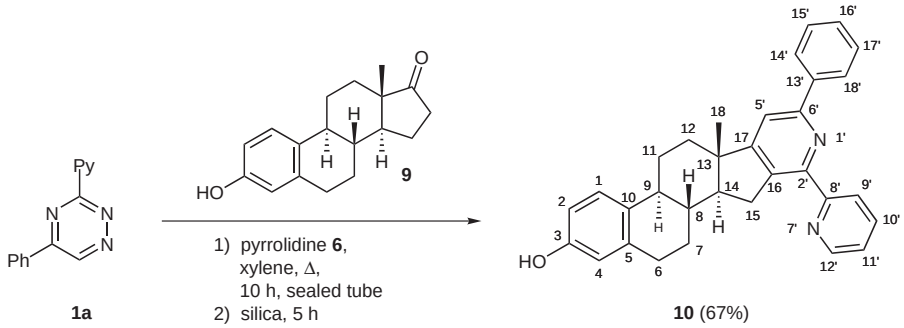


Entry	Ketone	Thermal conditions[a]	TIE (method A)[b]	Microwave conditions (method B)[a]	Silica method[a]
1	 **2a**	4 Å mol. sieves, $CHCl_3$, 62 °C, 48 h, 0%	4 Å mol. sieves, PhMe, 120 °C, 22 h, 74%	Neat, 120 °C, 20 min, 88%	Silica, PhMe, 120 °C, 5 h, 99%
2	 **2b**	–	4 Å mol. sieves, PhMe, 120 °C, 36 h, 79%	Neat, 150 °C, 30 min, 75%	Silica, PhMe, 120 °C, 5 h, 99%

[a] R_2NH = pyrrolidine.
[b] R_2NH = *N*-methylethane-1,2-diamine.

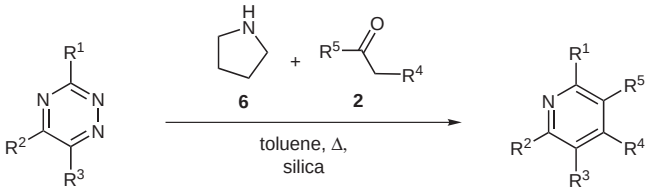
The overall effect of the silica is to increase the rate of the aromatisation–elimination step (see Scheme 1) without interfering with other phases of the cascade sequence. It seems likely that the heterogeneous, slightly acidic surface of the silica facilitates elimination–aromatisation.[7,8] The reaction proceeds in a range of solvents (toluene, chloroform, dichloromethane, and ethyl acetate) and does not seem to require strictly anhydrous conditions. However, anhydrous toluene is the solvent of choice. The results collected in Table 1 provide a comparison of the various procedures for the one-pot conversion of triazine **1a** into substituted pyridines **5a** and **5b** using cyclopentanone (**2a**) and cyclohexanone (**2b**), respectively. As can be seen, the silica method gives quantitative yields, even with the less reactive cyclohexanone (**2b**),[4e] with reaction times of only 5 hours. The silica reactions in Table 1 were carried out on a 0.2 mmol scale but larger-scale conversions are straightforward: thus, triazine **1a** (2.5 mmol) with cyclopentanone (**2a**) gave the desired pyridine **5a** in 89% isolated yield.

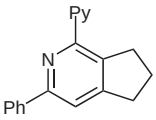
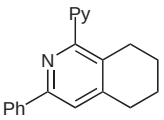
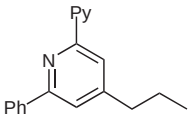
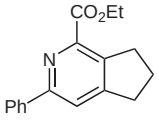
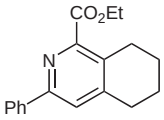
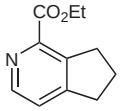
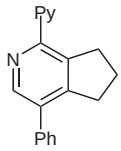
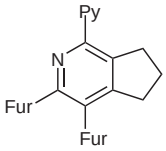
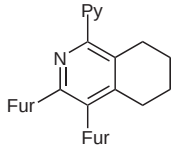
The scope of this improved methodology was established by carrying out the reaction with several mono-, di- and trisubstituted triazines **1** in combination with cyclopentanone (**2a**), cyclohexanone (**2b**), and valeraldehyde (**2c**, Table 2). In all of the examples studied, the yields were better or comparable to those obtained using the TIE or MW approaches.[2a–c] The previously observed reactivities were mirrored in the silica method: 5-phenyl-3-(pyridin-2-yl)-1,2,4-triazine (**1a**) and 5,6-di(furan-2-yl)-3-(pyridine-2-yl)-1,2,4-triazine (**1d**) were most reactive, while the 5-phenyl-1,2,4-triazine-3-carboxylic acid ethyl ester (**1b**) and the 1,2,4-triazine-3-carboxylic acid ethyl ester (**1e**) were less reactive, nevertheless providing good yields. It is worth noting that in some cases (entries 3, 6, 7, 8, and 9), higher reaction temperatures (160 °C) and a sealed tube were necessary in order to achieve optimal results.



Scheme 3

Table 2 Scope of Silica Method for Pyridines Synthesis



Entry	Triazine and ketone	Product[a,b]
1	**1a** R^1 = Py, R^2 = Ph, R^3 = H (**2a**) Cyclopentanone	 **5a**;[d] 120 °C, 5 h, 99%
2	**1a** R^1 = Py, R^2 = Ph, R^3 = H (**2b**) Cyclohexanone	 **5b**;[d] 120 °C, 5 h, 99%
3	**1a** R^1 = Py, R^2 = Ph, R^3 = H (**2c**) Valeraldehyde	 **5c**;[c] 160 °C, 10 h, 72%
4	**1b** R^1 = CO_2Et, R^2 = Ph, R^3 = H (**2a**) Cyclopentanone	 **5d**;[d] 120 °C, 10 h, 77%
5	**1b** R^1 = CO_2Et, R^2 = Ph, R^3 = H (**2b**) Cyclohexanone	 **5e**;[d] 120 °C, 10 h, 73%
6	**1e** R^1 = CO_2Et, R^2 = H, R^3 = H (**2a**) Cyclopentanone	 **5f**;[c] 160 °C, 10 h, 50%
7	**1c** R^1 = Py, R^2 = H, R^3 = Ph (**2a**) Cyclopentanone	 **5g**;[c] 160 °C, 10 h, 70%
8	**1d** R^1 = Py, R^2 = Fur, R^3 = Fur (**2a**) Cyclopentanone	 **5h**;[c] 160 °C, 2 h, 99%
9	**1d** R^1 = Py, R^2 = Fur, R^3 = Fur (**2b**) Cyclohexanone	 **5i**;[c] 160 °C, 5 h, 89%

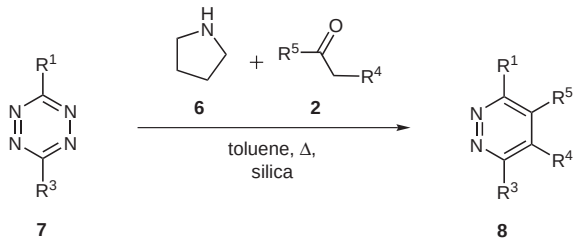
[a] Previously reported yield for TIE method (ref. 2a): **5a** 74%, **5b** 79%, **5c** n/a, **5d** 33%, **5e** 61%, **5f** 31%, **5g** n/a, **5h** 85%, **5i** 82%.
[b] Previously reported yield for MW method (ref. 2b): **5a** 77%, **5b** 73%, **5c** 81%, **5d** 67%, **5e** n/a, **5f** n/a, **5g** 64%, **5h** 91%, **5i** 64%.
[c] Reaction conditions: oil bath 160 °C, toluene, sealed tube.
[d] Reaction conditions: oil bath 120 °C, toluene, flask equipped with condenser.

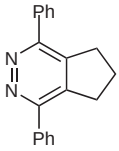
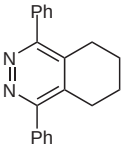
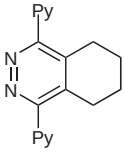
Similar inverse electron-demand Diels–Alder/retro-Diels–Alder–aromatisation sequences have been employed to convert tetrazines into pyridazines[9] and we have employed the TIE procedure to facilitate the aromatisation step.[2d] Table 3 illustrates that 3,6-diphenyl-1,2,4,5-tetrazine (**7a**) and 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (**7b**) can be converted into the corresponding pyridazines **8a**–**c** using the silica variant.

Recently, Potter et al. reported the preparation of E-ring-modified steroids for evaluation as inhibitors of 17β-hydroxysteroid dehydrogenase (17β-HSD) and commented on the inefficiency of routes to pyridine annelated analogues.[10] Inspired by this work we decided to utilise the silica gel method to prepare a novel steroidal pyridine (Scheme 3).

Thus, triazine **1a** was reacted with estrone (**9**) and pyrrolidine in a sealed tube for 10 hours, followed by treatment with silica in order to afford the novel E-ring-modified

Table 3 Scope of Silica Method for Pyridazine Synthesis



Entry	Tetrazine and ketone	Product[a]
1	**7a** R^1 = Ph, R^3 = Ph	
	(**2a**) Cyclopentanone	**8a**; 120 °C, 10 h, 98%
2	**7a** R^1 = Ph, R^3 = Ph	
	(**2b**) Cyclohexanone	**8b**; 120 °C, 15 h, 82%
3	**7b** R^1 = Ph, R^3 = Py	
	(**2b**) Cyclohexanone	**8c**; 160 °C, 4 h, 50%

[a] Previously reported yield for TIE method (ref. 2d): **11a** 93%, **11b** 85%, **11c** 41%.

steroid **10** in 67% yield (37% in refluxing conditions).[11] It should be noted that in this example an efficient conversion was observed only when the silica gel was added after the formation of the dihydropyridine intermediate[12] (in all the other cases all components were introduced at the commencement of the reaction).

In conclusion, a straightforward one-pot procedure for the preparation of highly substituted pyridines and pyridazines has been developed based on an in situ silica-mediated elimination–aromatisation step. The effectiveness and general applicability of this protocol has been demonstrated, indicating that the 'silica approach' is the method of choice for the preparation of highly substituted pyridines, especially on preparative scale.

Acknowledgment

We are grateful to the EPSRC (N.C. and W.J.B.), GlaxoSmithKline (W.J.B.) and Fond Special de Recherche, Université Catholique de Louvain (P.W.) for financial support.

References and Notes

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(5) Chenard, B. L.; Ronau, R. T.; Schulte, G. A. *J. Org. Chem.* **1988**, *53*, 5175.

(6) **Representative Procedure**
A suspension of triazine **1a** (50 mg, 0.21 mmol), pyrrolidine (**6**, 26 μL, 0.31 mmol), cyclopentanone (**2a**, 27 μL, 0.31 mmol) and silica (Fluka, flash chromatography silica gel 60, 220–440 mesh, 200 mg) in toluene (4 mL) was heated under reflux for 5 h. The reaction mixture was cooled to r.t., diluted with EtOAc (6 mL), and stirred an additional 20 min at the same temperature. The mixture was then filtered through a Celite pad, concentrated and the residue obtained was eluted from a column of silica (PE–EtOAc, 5:1) yielding the desired pyridine **5a** (57 mg, 99%); data were consistent with those reported in ref. 2b.

(7) Banerjee, A. K.; Laya, M. S.; Vera, W. J. *Russ. Chem. Rev.* **2001**, *70*, 971.

(8) Similar reactions were carried out in which the silica gel was replaced by stoichiometric amounts of HCl, MeCOOH, Et_3N, or 1,5-diazabicyclo[4.3.0]non-5-ene (DBU). None of these reactions produced pyridines **5** in significant quantities.

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(11) The structure of the cycloaddition product **10** was assigned using NOE and HMBC NMR experiments.

(12) A solution of triazine **1a** (100 mg, 0.43 mmol), pyrrolidine (**6**, 52 μL, 0.64 mmol) and estrone (**9**) (113 mg, 0.42 mmol) in xylene (4 mL) was heated in a screwcapped tube at 160 °C

for 10 h. The reaction mixture was cooled to r.t., silica (Fluka, flash chromatography silica gel 60, 220–440 mesh) was added and the yellow suspension obtained refluxed for an additional 5 h. The mixture was then cooled to r.t., filtered through a Celite pad, concentrated and the residue obtained was eluted from a column of silica ($CHCl_3$–EtOAc, 7:1) yielding the desired 3-hydroxy-estra-1,3,5 (10)-triene-[17,16-*c*]-(2′-pyrid-2-yl)-(6′-phenyl)-pyridine (**10**, 129 mg, 67%) as a white solid, mp 261–262 °C (toluene–hexane); $[\alpha]_D^{25}$ –50.0 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (1 H, ddd, *J* = 0.9, 1.8, 4.8 Hz, C-9′-H), 8.43 (1 H, ddd, *J* = 0.9, 1.0, 7.9 Hz, C-12′-H), 8.13 (2 H, m, C-14′-H, C-18′-H), 7.83 (1 H, ddd, *J* = 1.8, 7.6, 7.9 Hz, C-11′-H), 7.56 (1 H, s, C-5′-H), 7.49 (2 H, m, C-15′-H, C-17′-H), 7.41 (1 H, m, C-16′-H), 7.29 (1 H, ddd, *J* = 1.0, 4.8, 7.6 Hz, C-10′-H), 7.18 (1 H, d, *J* = 8.4 Hz, C-1-H), 6.63 (1 H, dd, *J* = 2.6, 8.4 Hz, C-2-H), 6.57 (1 H, d, *J* = 2.6 Hz, C-4-H), 4.80 (1 H, s, OH), 3.45 (1 H, dd, *J* = 5.8, 16.1 Hz, H-12a), 3.04 (1 H, dd, *J* = 11.9, 16.1 Hz, H-12b), 2.90 (2 H, m, H-6a,b) 2.47 (1 H, m), 2.35 (2 H, m), 2.12 (1 H, m), 1.77 (4 H, m), 1.50 (1 H, m), 1.07 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 158.6, 155.2, 153.8, 151.6, 148.5, 140.0, 138.71, 136.7, 136.4, 132.3, 128.6, 127.1, 126.3, 123.6, 122.9, 115.4, 113.3, 112.9, 56.1, 45.8, 44.3, 37.8, 34.6, 32.2, 29.6, 27.7, 26.4, 19.0. MS (EI): *m/z* (%) = 459.2 (100) [M + 1]. HRMS (EI): *m/z* calcd for $C_{32}H_{31}N_2O$ [M + 1]: 459.2436; found: 459.2431 (–3.2 ppm error).