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Improved Methodologies for the Preparation of Highly Substituted Pyridines

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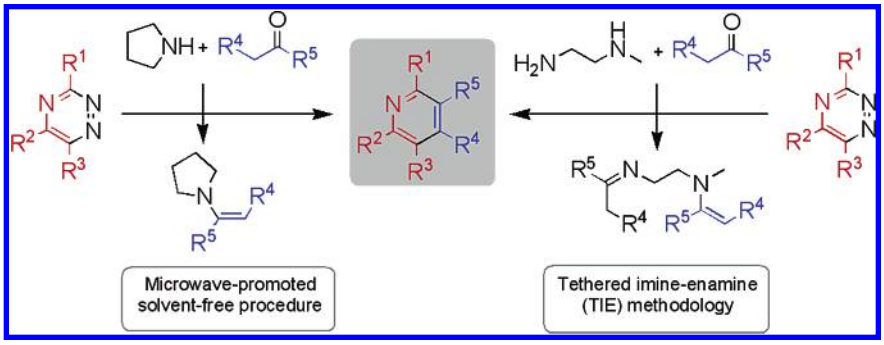

Two separate strategies have been developed for the preparation of highly substituted pyridines from 1,2,4-triazines via the inverse-electron-demand Diels−Alder reaction: a microwave-promoted, solvent-free procedure and a tethered imine-enamine (TIE) approach. Both routes avoid the need for a discrete aromatization step and offer significant advantages over the classical methods, giving a wide variety of tri-, tetra-, and penta-substituted pyridines in high, optimized yields.

Introduction

The wide-ranging biological activity associated with many pyridine derivatives, both naturally occurring and synthetic, ensures that the preparation of these important heterocyclic systems remains a current topic of interest.[1] For more than a century, many diverse methods have been developed to prepare pyridines with various ring substitution patterns.[1−3] As part of an ongoing research program into the synthesis of heterocyclic and heteroaromatic compounds,[4] we were interested in routes to highly substituted pyridines. In the search for a direct and convenient method, we considered the use of heterocyclic azadienes in Diels−Alder (DA) reactions, followed by either extrusion of part of the resulting bicycle in a retro-[4+2]-reaction or scission of the resulting

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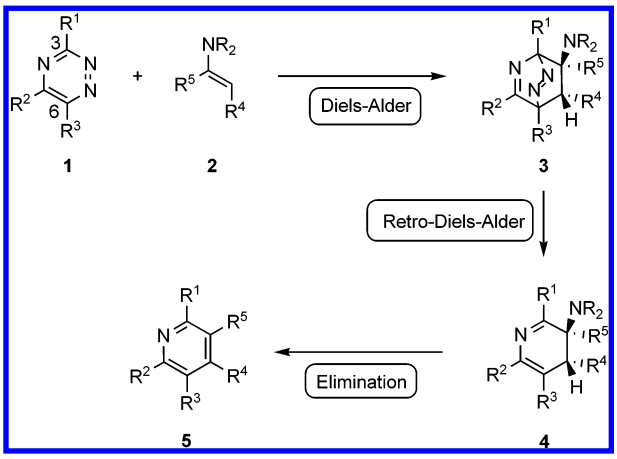
bridge.[5] Oxazoles were considered, but when reactions are carried out with these substrates, the fragmentation of the oxa-bridge can prove problematic.[5] Similarly, pyrimidines are capable of serving as pyridine precursors, but in this case the mode of cycloaddition (C-2/C-5 vs C-4/N-1) and the observed regioselectivity are dependent upon the dienophile employed, as well as the substitution pattern of the parent pyrimidine.[5]

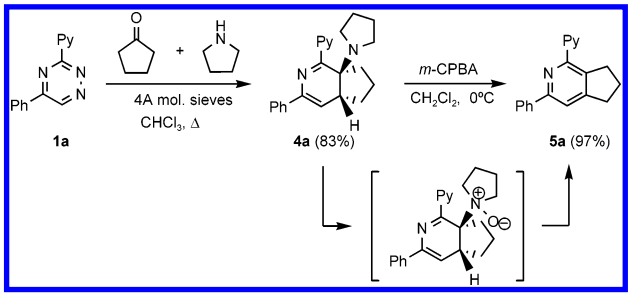
With 1,2,4-triazines **1**, addition across C-3/C-6 is nearly always favored.[6–9] One of the most popular versions of this reaction utilizes enamines **2** as dienophiles in an inverse-electron-demand Diels–Alder reaction, followed by in situ loss of nitrogen from **3** and subsequent elimination/aromatization (Scheme 1).[6,8,9] This classical methodology, widely used, had two main limitations, namely, the requirement for a preformed enamine and the unusual stability of the intermediate **4**, especially when using enamines derived from cyclohexanones.[6,8] Boger et al. circumvented these difficulties for 1,2,4-triazine and 3-substituted-1,2,4-triazines by the addition of 4A molecular sieves, which allowed in situ enamine formation and catalyzed the elimination step, forming pyridine **5** from dihydropyridine **4**, although yields remained low (19–66%).[9]

SCHEME 1



However, when we tried to apply the methodology developed by Boger et al. to disubstituted 1,2,4-triazines (e.g., **1a**,[10] Scheme 2), we found that although the DA/retro-DA sequence proceeded smoothly, in situ aromatization was not observed and the dihydropyridine intermediate (e.g., **4a**) was isolated in excellent yield. Aromatization of **4a** to **5a** was accomplished in a separate step via Cope elimination[8i] of the corresponding *N*-oxide intermediate (Scheme 2).

SCHEME 2



Ideally, we required a procedure that could be utilized to prepare these more substituted pyridines without the need to employ a discrete aromatization step (particularly one requiring the use of a peracid). This paper describes two complementary procedures for the "one-pot" synthesis of highly substituted pyridines, one employing microwave irradiation as the key technological advance, and the second approach based on tethered imine-enamine (TIE) methodology.[11]

Results and Discussion

Highly Substituted Pyridines via Solvent-Free Microwave Synthesis. The present investigation commenced with the search for improved reaction conditions for the direct synthesis of highly substituted pyridines from 1,2,4-triazines **1**. In certain published examples higher temperatures (and the addition of carboxylic acids) have been shown to facilitate elimination to give pyridines,[8e,9c] and so we first investigated if this would solve the problematic elimination step en route to highly substituted pyridines. We therefore took 5,6-difuran-2-

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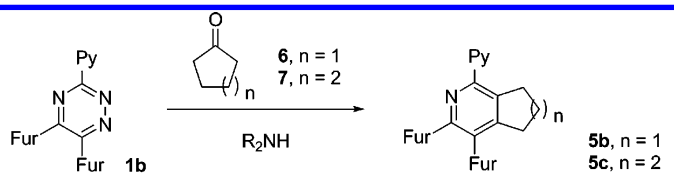
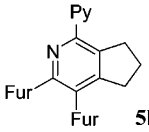
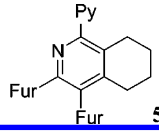
TABLE 1. Formation of Pentasubstituted Pyridines 5b, 5c from Triazine 1b[a]



Entry	Ketone	Amine	Product	A Thermal conditions[b]	B Microwave conditions[c] (solution)	C Microwave conditions[c] (neat)
i	 6		 5b	PhMe, Δ, 13 h, 89%[d]	PhMe, 120°C 90 min, 83%	120°C 20 min, 91%
ii	6		5b	PhMe, Δ, 25 h, 86%		120°C 30 min, 83%
iii	6		5b	PhMe, Δ, 20 h, 81%		120°C 30 min, 74%
iv	6	Me_2NH	5b	PhMe, Δ, 96 h, 50%[e,f]	THF, 150°C 40 min, 80%	-
v	6	Et_2NH	5b	PhMe, Δ, 25 h, 68%[e]		150°C 60 min, 74%[e]
vi	6	Bu_2NH	5b	PhMe, Δ, 36 h, 63%[e]		-
vii	6	Cy_2NH	5b	PhMe, Δ, 96 h, 49%[e]		150°C 90 min, 61%[e]
viii	 7		 5c	PhMe, Δ, 96 h, 25%[e]		120°C 20 min, 64%

[a] Isolated yield based on the starting 1,2,4-triazine **1b**. [b] All reactions utilized 1,2,4-triazine **1b** (0.1 mmol), ketone (0.1 mmol), the specified amine (0.1 mmol), and 4A molecular sieves (0.100 g) in toluene (0.2 mL) at reflux. [c] Microwave reactions were carried out by irradiating a mixture of 1,2,4-triazine **1b** (0.1 mmol), amine (0.1 mmol) and ketone (0.1 mmol) (power = 150−200 W). [d] In refluxing $CHCl_3$: 37%, 13 h. [e] 1,2,4-Triazine **1b** was present in the unpurified product (^{1}H NMR spectroscopy). [f] 61% when excess dimethylamine was employed.

yl-3-pyridin-2-yl-[1,2,4]triazine **1b**[12] and investigated its reaction with cyclopentanone (1 equiv) and pyrrolidine (1 equiv) in the presence of 4A molecular sieves. When the reaction was performed in toluene under reflux instead of chloroform at 55 °C, the desired pyridine **5b** was obtained in a yield of 89% (in chloroform the yield was 37% after 13 h at reflux). With this result in hand, we went on to optimize this methodology, first in terms of the amine. A series of commercially available cyclic and acyclic secondary amines was reacted with triazine **1b** and cyclopentanone or cyclohexanone under the conditions described above.

As illustrated in Table 1 (column A), cyclic amines (entries i−iii) were shown to be more efficient than acyclic ones (entries iv−vii) in reactions with cyclopentanone: in the latter cases longer reaction times were needed and unreacted triazine was recovered in all examples. The order of reactivity with cyclopentanone was estimated as pyrrolidine (entry i) > morpholine (entry ii) ≈ piperidine (entry iii) > diethylamine (entry v) > dibutylamine (entry vi) > dicyclohexylamine (entry vii) ≈ dimethylamine (entry iv), which presumably, for the most part, reflects steric effects in enamine formation and in the subsequent cycloaddition reactions. The lower reactivity of dimethylamine could be due to its high volatility, and some improvement in yield was observed when a large excess of the amine was employed. The higher reactivity of the pyrrolidine enamine compared to the piperidine or morpholine analogues is well-precedented.[9c,13]

Cyclohexanone has always[8e,9b,c,i] proved to be a problematic substrate in these cycloaddition reactions, and this was the case in the preparation of tetrahydroisoquinoline **5c** from triazine **1b** using pyrrolidine (entry viii): pyridine **5c** was obtained in only 25% yield even after prolonged heating (96 h). Such results have been rationalized in terms of the exceptional stability of the

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intermediate dihydropyridine **4**, where the alignment between the crucial hydrogen and nitrogen atoms is particularly poor for E2 elimination.[8i,9b,c]

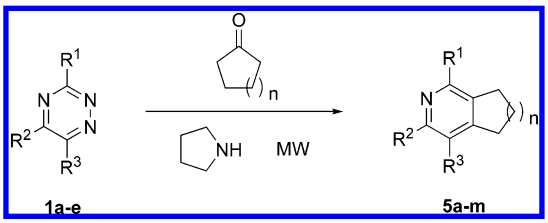
Despite these encouraging results using elevated temperatures, the reaction times with cyclopentanone-derived enamines were still long, and the yields of pyridines using enamines derived from cyclohexanone were disappointing. In view of the current interest in the use of microwave (MW) irradiation to expedite synthetic transformations,[14,15] we explored its use in these processes (Table 1, columns B and C). The first attempt involved treatment of a mixture of 1,2,4-triazine **1b**, pyrrolidine (1 equiv), and cyclopentanone (1 equiv) in toluene, in a focused monomode microwave reactor at a fixed temperature (120 °C) in a sealed vessel. After 90 min of irradiation, analysis of the unpurified reaction mixture by ^{1}H NMR spectroscopy showed pyridine **5b** to be the only product, and the isolated yield was 83% (Table 1B, entry i). This acceleration (13 h to 90 min) was dramatic but by repeating the process in a solvent-free environment,[14d−g] an even faster conversion was achieved. The optimum solvent-free process gave pentasubstituted pyridine **5b** in 91% yield after irradiation in the microwave reactor for just 20 min (Table 1C, entry i). This reaction was repeated with other disubstituted amines (Table 1C, entries ii−vii), but once again pyrrolidine proved to be the amine of choice.

We therefore studied the problematic reaction of triazine **1b** with cyclohexanone and pyrrolidine under solvent-free, microwave conditions (Table 1C, entry viii). We were delighted to find that the kinetic microwave effect was observed here too, as cyclohexa-annelated pyridine **5c** was formed in 64% yield after just 20 min reaction time (compared to 25% yield after 96 h reflux in toluene in the thermal process).

Given the success of solvent-free microwave technology using pyrrolidine in these preliminary studies, we went on to examine the scope of this method with respect to the 1,2,4-triazine and ketone. Thus, a range of triazines **1a**−**1e**[16] (0.1 mmol), ketones (0.1−0.2 mmol), and pyrrolidine (0.1−0.2 mmol) were subjected to microwave irradiation (Table 2). As can be seen, the methodology was successful, with all five triazines investigated giving tri-, tetra-, and pentasubstituted pyridines **5a**−**5m** in moderate to good yields (64−91%). The method was compatible with cyclopentanone, cyclohexanone, cycloheptanone, cyclooctanone, and cyclododecanone. In many of the MW-mediated pyridine syntheses utilizing 5-phenyl-3-(pyridin-2-yl)-1,2,4-triazine **1a**, an easily separable, minor byproduct was observed that contained both a polysubstituted pyridine nucleus and a pyrrolidine substituent. In the reaction of cyclopentanone with **1a** (entry i), this product was isolated (9%), fully characterized, and shown to be 3-phenyl-1-(pyridin-2-yl)-4-(pyrrolidin-1-yl)-6,7-dihydro-5*H*-[2]pyrindine (**5a**, R^3 = pyrrolidinyl), presumably formed by nucleophilic addition of a second pyrrolidine to intermediate **4a** prior to aromatization.

All of the examples in Table 2 utilized cyclic ketones as enamine precursors, thereby removing regioselectivity issues as, after aromatization, single products were obtained. However, with unsymmetrical enamines, the regioselectivity of the [4+2]-cycloaddition reaction becomes an interesting issue. Consequently, a series of unsymmetrical ketones, acyclic ketones, and aldehydes was reacted with pyrrolidine and different 1,2,4-triazines under solvent-free, microwave conditions (Table 3). As can be seen, these reactions almost all give useful yields of the corresponding pyridines and in many cases proceed with high or complete regioselectivity. In reactions with 3-pyridyl-5-phenyl-1,2,4-triazine **1a**, preferential addition of the nucleophilic carbon of the enamine occurs at the C-6 center to give a predominance of isomers **8**, and with ketones **10** and **12**, together with both aldehydes, the process is completely regioselective. Of course, the C-3 triazine center is also electrophilic, but presumably in triazine **1a** the fact that C-6 is unsubstituted is of overriding importance, with other factors, such as π-stacking and electronic interactions, influencing the exact ratio of regioisomers in cases where a mixture is obtained.[17]

TABLE 2. Solvent-Free, Microwave Preparation of Pyridines 5[a,b]



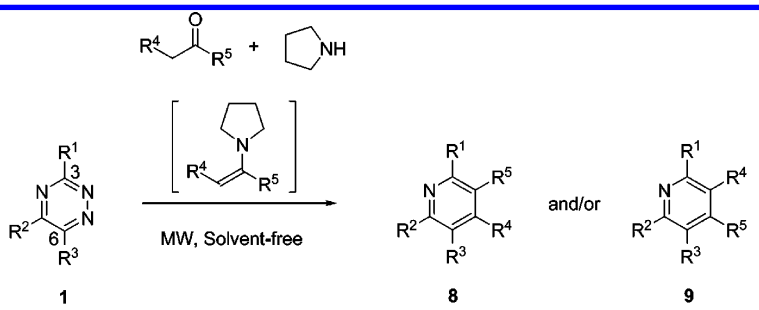
entry	triazine	R^1	R^2	R^3	*n*	temp (°C)	time (min)	pyridine	yield (%)
i[c]	**1a**	Py	Ph	H	1	120	20	**5a**	88%
ii	**1b**	Py	Fur	Fur	1	120	20	**5b**	91
iii	**1c**	CO_2Et	Ph	H	1	120	30	**5d**	67
iv	**1d**	CO_2Et	Me	Me	1	160	90	**5e**	82
v	**1e**	Py	H	H	1	120	15	**5f**	85
vi	**1a**	Py	Ph	H	2	150	30	**5g**	75
vii	**1b**	Py	Fur	Fur	2	120	20	**5c**	64
viii	**1e**	Py	H	H	2	150	15	**5h**	75
ix	**1a**	Py	Ph	H	3	120	30	**5i**	91
x	**1b**	Py	Fur	Fur	3	120	30	**5j**	69
xi	**1e**	Py	H	H	3	120	15	**5k**	82
xii	**1a**	Py	Ph	H	4	120	30	**5l**	80
xiii	**1a**	Py	Ph	H	8	150	30	**5m**	81

[a] Isolated yield based on the starting 1,2,4-triazine **1**. [b] All reactions were carried out by microwave irradiation (power = 150−200 W) of a mixture of 1,2,4-triazine **1** (0.1 mmol), ketone (0.1 mmol) and pyrrolidine (0.1 mmol). [c] **5a** (R^3 = pyrrolidine) was obtained as a minor byproduct (9%).

(14) For recent reviews, see: (a) de la Hoz, A.; Díaz-Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34,* 164−178. (b) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43,* 6250−6284. (c) Nüchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.* **2004**, *6,* 128−141. (d) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002. (e) Varma, R. S. *Pure Appl. Chem.* **2001**, *73,* 193−198. (f) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100,* 1025−1074. (g) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213−1234.

(15) For recent use of microwave in cycloaddition reactions and heterocyclic synthesis, see: (a) Loupy, A.; Maurel, F.; Sabatié-Gogová, A. *Tetrahedron* **2004**, *60*, 1683−1691. (b) Siu, J.; Baxendale, I. R.; Ley, S. V. *Org. Biomol. Chem*. **2004**, *2*, 160−167. (c) Minetto, G.; Raveglia, L. F.; Taddei, M. *Org. Lett*. **2004**, *6*, 389−392. (d) Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. H.; Wang, Y.; Zhao, Z.; Lindsley, C. W. *Org. Lett*. **2004**, *6*, 1453−1456. (e) Bashiardes, G.; Safir, I.; Mohamed, A. S.; Barbot, F.; Laduranty, J. *Org. Lett*. **2003**, *5*, 4915−4918. (f) Surya Prakash Rao, H.; Jothilingam, S. *J. Org. Chem*. **2003**, *68*, 5392−5394. (g) Van der Eycken, E.; Appukkuttan, P.; Borggraeve, W. D.; Dehaen, W.; Dallinger, D.; Kappe, C. O. *J. Org. Chem*. **2002**, *67*, 7904−7907. (h) Trost, B. M.; Crawley, M. L. *J. Am. Chem. Soc*. **2002**, *124*, 9328−9329. de la Hoz, A.; Díaz-Ortiz, A.; Moreno, A.; Langa, F. *Eur. J. Org. Chem*. **2000**, 3659−3673. (i) Avalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Jiménez, J. L. Palacios, J. C.; Sánchez, J. B. *J. Org. Chem*. **1999**, *64*, 6297−6305.

TABLE 3. Solvent-Free, Microwave Preparation of Pyridines 8 and 9 from Unsymmetrical Enamines[a–c]

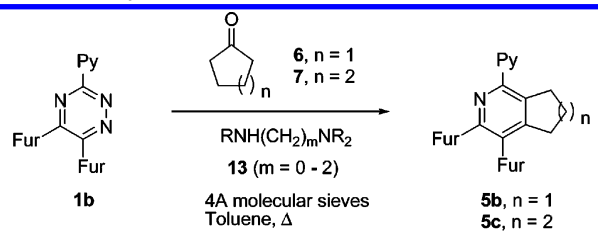


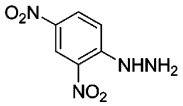
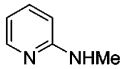
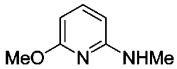
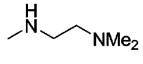
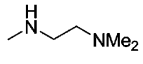
Entry	Triazine	Ketone	Temp	Time	Products	Yield (8:9)
i	**1a**	**10**	120ºC	30 min	**8a**	78%
ii	**1a**	**11**	150ºC	60 min	**8b** **9b**	40% 2:1
iii	**1a**	**12**	150ºC	60 min	**8c**	66%
iv	**1a**		120ºC	30 min	**8d** **9d**	71% 6:1
v	**1a**		120ºC	60 min	**8e** **9e**	60% 2:1
vi	**1a**		120ºC	30 min	**8f**	81%
vii	**1a**		120ºC	15 min	**8g (= 9d)**	85%
viii	**1b**		120ºC	60 min	**9h**	69%
ix	**1b**		120ºC	15 min	**9i**	82%
x	**1e**		150ºC	15 min	**9j**	67%

[a] Isolated yield based on the starting 1,2,4-triazine **1**. [b] All reactions were carried out by microwave irradiation (power = 150−200 W) of a mixture of 1,2,4-triazine **1** (0.1 mmol), ketone or aldehyde (0.2 mmol), and pyrrolidine (0.2 mmol). [c] The regiochemistries were established by NOE experiments.

The regioselective formation of pyridine **9j** from 3-(pyridin-2-yl)-1,2,4-triazine **1e** (also unsubstituted at C-6) follows the same pattern (entry x). It should be noted that, whereas the reaction of triazine **1a** with acetophenone gave a mixture of regioisomeric products (entry iv), the use of phenylacetaldehyde gives 2,4-diphenyl-6-(pyridin-2-yl)-pyridine **8g** exclusively (entry vii). However, with triazine **1b**, the C-6 position is substituted and

TABLE 4. Formation of Pentasubstituted Pyridines 5b, 5c from Triazine 1b via Tethered-Base Approach



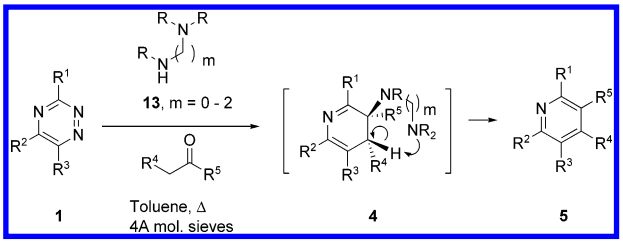
Entry[a]	"Diamine"	Ketone	Time	Product	Yield[b]
i	 **13a**	 **6**	96 h	**5b**	15%[c]
ii	$PhCH_2NHNMe_2$ **13b**	**6**	96 h	**5b**	35%[c]
iii	 **13c**	**6**	96 h	**5b**	-[d]
iv	 **13d**	**6**	96 h	**5b**	-[d]
v	 **13e**	**6**	20 h	**5b**	88%
vi	 **13e**	 **7**	36 h	**5c**	34%

[a] All of the reactions utilized 1,2,4-triazine **1b** (0.1 mmol), ketone (0.2 mmol), and diamine (0.2 mmol) in the presence of 4A molecular sieves (0.1 g) in toluene (1 mL) at reflux. [b] Isolated yield based on the starting 1,2,4-triazine **1b**. [c] 1,2,4-Triazine **1b** was present in the unpurified product (^{1}H NMR spectroscopy). [d] ^{1}H NMR spectroscopic analysis of the unpurified (concentrated) reaction mixture showed only 1,2,4-triazine **1b**.

the enamine carbon attaches preferentially to the C-3 position (entry ix; the fact that the C-3 substituent is electron-withdrawing in both cases may also be an important factor).

Highly Substituted Pyridines via Tethered Imine-Enamine (TIE) Methodology. Microwave technology therefore proved useful for the conversion of 1,2,4-triazines into a wide range of pyridines in acceptable times and yields. Despite the many advantages of this technology, however, the prospect of carrying out such chemistry on a large scale is limited, since the dedicated single-mode microwave instruments available today process only small reaction volumes under sealed-vessel conditions. Therefore, we turned our attention to the development of novel thermal procedures that would be amenable to scale-up. The first approach explored is illustrated in Scheme 3. We reasoned that by replacing the amine normally used for enamine formation, with a suitable diamine **13**, an intermediate dihydropyridine **4** would be formed that may be capable of intramolecular deprotonation at the allylic position, thus aiding the elimination step. This could allow, for instance, either an E1cb mechanism (if the anion was sufficiently stable) or epimerization of this carbon center, leading to an *anti*-arrangement of proton and adjacent leaving group and hence a facile E2 elimination. In pursuit of this "tethered-base" approach, a series of hydrazines and diamines (i.e., $m = 0-2$) was treated with a solution of triazine **1b** and cyclopentanone in the presence of 4A molecular sieves in toluene at reflux (Table 4).

SCHEME 3



(16) **1a**: ref 10. **1b**: ref 12. **1c**: Benson, S. C.; Gross, J. L.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 3257−3269. **1d**: Pendrak, I.; Barney, S.; Wittrock, R.; Lambert, D. M.; Kingsbury, W. D. *J. Org. Chem.* **1994**, *59*, 2623−2625. **1e:** Sauer, J.; Heldmann, D. K.; Pabst, G. R. *Eur. J. Org. Chem.* **1999**, 313−321.

(17) For cycloadditions to 1,2,4-triazines that result in regioisomeric mixtures, see refs 5−7 and (a) Neunhoeffer, H.; Fruhauf, H.-W. *Liebigs Ann. Chem.* **1972**, *758*, 120−124. (b) Müller, K.; Sauer, J. *Tetrahedron Lett.* **1984**, *25*, 2541−2544. (c) Boger, D. L.; Duff, S. R.; Panek, J. *S.*; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5782−5789. (d) d'A. Rocha Gonsalves A. M.; Pinho e Melo, T. M. V. D.; Gilchrist, T. L. *Tetrahedron* **1993**, *49*, 5277−5290 and references therein.

Unfortunately, with hydrazines (entries i, ii) and 2-aminopyridines (entries iii, iv), pyridine **5b** was only obtained in low yields (15−35%) after heating for 96 h, with unreacted triazine **1b** still present. In contrast, *N,N′,N′*-trimethylethylenediamine with cyclopentanone gave an 88% yield of pyridine **5b** with a reaction time of 20 h (entry v). When this approach was tried using cyclohexanone as substrate, however, the conversion into tetrahydroisoquinoline **5c** was again slow and low-yielding (entry vi).

As this initial tethered-base approach did not appear to be generally useful, we sought to design an alternative

SCHEME 4

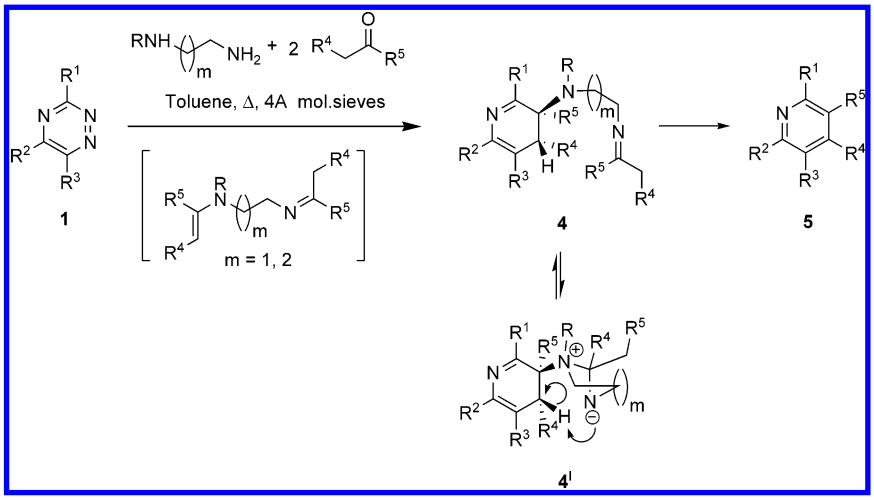
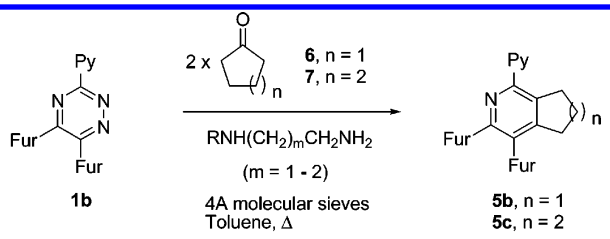


TABLE 5. Formation of Pentasubstituted Pyridines 5b, 5c from Triazine 1b via TIE Methodology



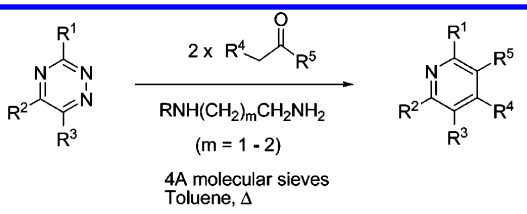
Entry[a]	Diamine	Ketone	Time	Product	Yield[b]
i	MeNH, NH_2	**6**	22 h	**5b**	88%
ii	PhNH, NH_2	**6**	24 h	**5b**	75%
iii	NHMe, NH_2	**6**	36 h	**5b**	10%[c]
iv	MeNH, NH_2	**6**	96 h	**5b**	85%
v	MeNH, NH_2	**7**	21 h	**5c**	82%
vi	MeNH, NH_2	**7**	24 h	**5c**	79%

[a] All of the reactions utilized 1,2,4-triazine **1** (0.1 mmol), ketone (0.6 mmol), and diamine (0.3 mmol) in the presence of 4A molecular sieves (0.1 g) in toluene (1 mL) at reflux. [b] Isolated yield based on the starting 1,2,4-triazine **1b**. [c] ^{1}H NMR spectroscopic analysis of the unpurified product showed the presence of unreacted 1,2,4-triazine **1b**.

system that would facilitate the elimination/aromatization step. Thus, a tethered imine-enamine (TIE) concept was designed in which a diamine would be employed that could react with 2 equiv of the ketone to generate an enamine linked to a tethered imine (Scheme 4). The idea was that the intermediate imine **4** could provide a tethered base as before but also that it could potentially mimic the *N*-oxide used in the Cope elimination (Scheme 2), by generating in situ the zwitterionic species **4′**. Thus, zwitterion **4′** could facilitate elimination to the corresponding pyridine (by allowing an E1cb mechanism or epimerizing adjacent to the amine leaving group).

We investigated this new variant by studying the reaction of triazine **1b** (0.1 mmol) with cyclopentanone (0.6 mmol) in the presence of several *N*-substituted diamines (0.3 mmol) as shown in Table 5 (entries i−iv). Initial experiments were carried out using *N*-methylethylenediamine due to its commercial availability and the fact that the two-carbon tether allows a favorable six-membered transition state in **4′**. In chloroform at vigorous

TABLE 6. Formation of Pentasubstituted Pyridines via TIE Methodology



Entry[a]	Triazine	R^1	R^2	R^3	Ketone	Time	Product	Yield[b]
i	**1a**	Py	Ph	H	**6**	22 h	**5a**	74%
ii	**1a**	Py	Ph	H	**7**	36 h	**5g**	79%
iii	**1a**	Py	Ph	H		22 h	**5i**	100%
iv	**1a**	Py	Ph	H		21 h	**5l**	77%
v	**1a**	Py	Ph	H		24 h	**5m**	-[c]
vi	**1a**	Py	Ph	H		46 h	**8e**	59%
vii	**1b**	Ph	Fur	Fur	**6**	22 h	**5b**	88%
viii	**1b**	Ph	Fur	Fur	**7**	22 h	**5c**	82%
ix	**1c**	CO_2Et	Ph	H	**6**	6 h	**5d**	33%
x	**1c**	CO_2Et	Ph	H	**7**	16 h	**5n**	61%

[a] All of the reactions utilized 1,2,4-triazine **1** (0.1 mmol), ketone (0.6 mmol), and diamine (0.3 mmol) in the presence of 4A molecular sieves (0.1 g) in toluene (1 mL) at reflux. [b] Isolated yield based on the starting 1,2,4-triazine **1**. [c] ^{1}H NMR spectroscopy and analysis of the crude reaction product showed only unreacted 1,2,4-triazine **1a** (even after 76 h at reflux).

reflux no reaction was observed, but in refluxing toluene the expected pyridine **5b** was isolated in excellent yield (88%) after 22 h (entry i). Three other diamines were studied in the same process with yields ranging from 10% to 85% (entries ii−iv), but only *N*-methylpropylenediamine gave comparable results (85%, entry iv). In view of this success, *N*-methylethylenediamine and *N*-methylpropylenediamine were employed in the corresponding reactions using cyclohexanone (entries v and vi). We were delighted to obtain tetrahydroisoquinoline **5c** in good yield (82% and 79%, respectively).

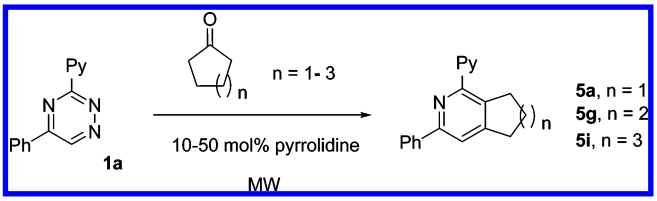
The combination of thermal conditions, high yields and reasonable reaction times (compare to Tables 1 and 3), together with the successful use of the problematic cyclohexanone substrate, suggested that the TIE methodology could provide a general procedure to prepare highly substituted pyridines. We therefore went on to study the scope of the methodology with respect to the ketone and the 1,2,4-triazine components, using *N*-methylethylenediamine as the preferred diamine (Table 6). With triazine **1a** and cyclopentanone, cyclohexanone, cycloheptanone, and cyclooctanone, the corresponding pyridines **5a**, **5g**, **5i**, and **5l** were formed in good to quantitative yields (entries i−iv). With cyclododecanone (entry v), none of the desired pyridine was obtained, even after extended reaction times, presumably due to steric factors: this result should be contrasted with the successful microwave-mediated process (Table 2, entry xiii). Triazine **1a** was also reacted with pentan-3-one under TIE conditions, giving only 3-ethyl-4-methyl-6-phenyl-2-(pyridin-2-yl)pyridine **8e** (entry vi); this contrasts to the microwave procedure, which gave a 2:1 mixture of two regioisomeric products (Table 3, entry v).

1,2,4-Triazines **1b** and **1c** are also good substrates for this TIE chemistry (entries vii−x). The most noteworthy feature of these results, however, is that tetrahydroisoquinolines **5g**, **5c**, and **5n** are accessible from 1,2,4-triazines and cyclohexanone in a one-pot, thermal procedure in good isolated yields (61−82%, entries ii, viii, and x); this constitutes a notable improvement to the traditional procedures.

Development of a Pyridine Synthesis using Substoichiometric Quantities of Amine. The inverse-electron-demand Diels−Alder reaction of 1,2,4-triazines and enamines formed in situ can, in principle, be catalytic in terms of amine.[9b] Such a variant of the TIE methodology would offer several advantages: for example, reduced amounts of amine and ketone would be required, and byproducts and waste would be reduced. Hence, triazine **1a** was reacted with cyclopentanone (3 equiv) and just 20 mol % of *N*-methylethylenediamine in toluene at reflux. After 4 days, an analysis of the reaction product by ^{1}H NMR spectroscopy indicated that the starting triazine **1a** and pyridine **5a** were present in a ratio of ca. 2:1. Thus, although partially successful, this version was simply too slow to be practical.

We therefore returned to the solvent-free, microwave procedure utilizing triazine **1a** (0.1 mmol), cyclopentanone (0.1 mmol), and different amounts of pyrrolidine (50, 20, or 10 mol %), which were subjected to microwave irradiation at 120 °C for the times indicated in Table 7 (entries i−iii). In all cases pyridine **5a** was obtained as the sole reaction product, but as expected, longer reaction times were required as the amount of pyrrolidine was decreased. However, with 20 mol % pyrrolidine (entry ii) the yield of 73% in 120 min compared reasonably well with the 88% yield in 20 min obtained using an equimolar amount of amine. Similar results were found with cyclohexanone (entry iv) and cycloheptanone (entry v) using 20 mol % of pyrrolidine. Thus, the amount of pyrrolidine used in the solvent-free microwave procedure can be reduced to substoichiometric quantities with only small reductions in yield, but this advantage is off-set by the longer reaction times.

TABLE 7. Solvent-Free, Microwave-Assisted Pyridine Formation Using Substoichiometric Quantities of Pyrrolidine



entry	pyrrolidine (mol %)	temp (°C)	time (min)	product	Yield[a] (%)
i	50	120	60	**5a**	77[b]
ii	20	120	120	**5a**	73
iii	10	120	240	**5a**	65
iv	20	150	160	**5g**	42
v	20	120	120	**5i**	85

[a] Isolated yield based on the starting 1,2,4-triazine **1a**. [b] 88% in 20 min using 1.0 equiv of pyrrolidine at 120 °C. [c] 75% yield in 30 min using 1.0 equiv of pyrrolidine at 150 °C. [d] 91% yield in 30 min using 1.0 equiv of pyrrolidine at 120 °C.

Summary

In summary, two novel protocols have been developed for the direct conversion of 1,2,4-triazines into highly substituted pyridines via the inverse-electron-demand Diels−Alder reaction. Both variants avoid the need for a separate aromatization step. The microwave-assisted, solvent-free route affords highly substituted pyridines in good to quantitative yields with relatively short reaction times. Furthermore it offers economic and ecological advantages, particularly when the substoichiometric base variant is employed. The TIE methodology also allows access to highly substituted pyridines in an operationally simple thermal process that should be amenable to larger scale production. Further studies on the applications of these methodologies to the synthesis of natural products are currently underway in our laboratories.

Experimental Section

Representative Procedures. Preparation of 3,4-di(furan-2-yl)-1-(pyridin-2-yl)-5,6,7,8-tetrahydroisoquinoline **5c**.

(a) Using Microwave-Promoted, Solvent-Free Conditions. 5,6-Di(furan-2-yl)-3-(pyridin-2-yl)-1,2,4-triazine **1b** (0.029 g, 0.1 mmol), pyrrolidine (0.009 mL, 0.1 mmol), and cyclohexanone (0.010 mL, 0.1 mmol) were mixed together into a 10 mL glass vessel sealed with a septum and irradiated at 120 °C (power 150−200 W). After 20 min, the vessel was cooled and diluted with dichloromethane (ca. 1 mL). followed by concentration in vacuo and purification by flash chromatography on silica gel (petroleum ether.ethyl acetate, 4:1) to give the title compound **5c** (0.022 g, 64%) as a white solid: mp 141−142 °C (hexane−$CHCl_3$); ν_{max} (film) 2932, 1588, 1536, 1409, 1151, 1016, 801, 743 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.67 (1 H,

ddd, J = 4.8, 1.2, 0.8 Hz), 7.85−7.79 (2 H, m), 7.60 (1 H, dd, J = 2.0, 0.8 Hz), 7.42 (1 H, dd, J = 2.0, 0.8 Hz), 7.30 (1 H, ddd, J = 6.4, 4.8, 1.6 Hz), 6.56 (1 H, dd, J = 3.2, 2.0 Hz), 6.32−6.29 (2 H, m) 5.79 (1 H, dd, J = 3.2, 0.8 Hz), 2.91 (2 H, t, J = 6.4 Hz), 2.62 (2 H, t, J = 6.0 Hz), 1.80−1.68 (4 H, m); δ_C (100 MHz, $CDCl_3$) 158.9 (C), 156.8 (C), 152.0 (C), 149.5 (C), 149.4 (C), 148.3 (CH), 145.7 (C), 142.9 (CH), 142.3 (CH), 136.7 (CH), 130.3 (C), 124.7 (CH), 123.0 (C), 122.8 (CH), 111.2 (CH), 111.2 (CH), 110.3 (CH), 109.7 (CH), 27.8 (CH_2), 27.2 (CH_2), 22.4 (CH_2), 22.0 (CH_2); *m/z* (EI) 342 (100%, M^+) [HRMS (EI) calcd for $C_{22}H_{18}N_2O_2$ 342.1368, found 342.1362 (1.8 ppm error)].

(b) Using Tethered Imine-Enamine (TIE) Methodology. A mixture of 5,6-di(furan-2-yl)-3-(pyridin-2-yl)-1,2,4-triazine **1b** (0.029 g, 0.1 mmol), *N*-methylethylenediamine (0.026 mL, 0.30 mmol), cyclohexanone (0.060 mL, 0.6 mmol), and powdered 4A molecular sieves (0.100 g) in toluene (1.0 mL) was heated at 120 °C for 21 h. The reaction was then cooled, filtered through a cotton wool plug, and concentrated in vacuo, to furnish the crude product. Purification by flash chromatography on silica gel (petroleum ether:ethyl acetate, 4:1) gave the title compound **5c** (0.028 g, 82%) with properties identical to those of the sample in part (a).

Acknowledgment. We are grateful to the EPSRC (S.A.R.) and the University of York (Y.F.S.) for financial support.

Supporting Information Available: Experimental procedures, data, and ^1H and ^{13}C NMR spectra for all novel substituted pyridines **5**, **8**, and **9** (27 compounds in total). This material is available free of charge via the Internet at http://pubs.acs.org.

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