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Synthesis of highly-functionalised pyridines via hetero-Diels–Alder methodology: reaction of 3-siloxy-1-aza-1,3-butadienes with electron deficient acetylenes

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Abstract—The hetero-Diels–Alder reaction between 1-aza-3-siloxy-1,3-butadienes and electron deficient acetylenes is described. The reactivity of a range of α,β-unsaturated oximes and hydrazones is assessed in the synthesis of tri- and tetra-substituted pyridines bearing an oxygen functionality at C-3. Microwave irradiation has been employed to decrease the extended reaction times and increase the poor yields often associated with this reaction.
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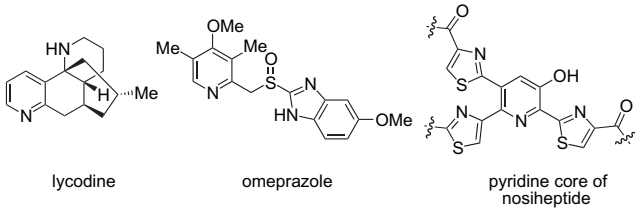
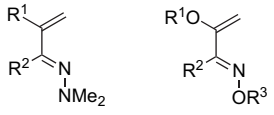
1. Introduction

The pyridine ring appears in a range of bioactive compounds, both naturally occurring and synthetic, often in highly substituted form; examples include the lycopodium alkaloids such as lycodine,[1] and the well-known proton-pump inhibitor omeprazole. Our own particular interest lies in the thiopeptide antibiotics, a class of sulfur containing highly modified cyclic peptides characterised by the presence of a heterocyclic centrepiece consisting of a tri- or tetra-substituted pyridine embedded in a macrocyclic array.[2] Examples of these types of natural products are amythiamicin D,[3] recently synthesised in our laboratory,[4] and nosiheptide.[5] In our synthesis of amythiamicin D, the pyridine core was successfully constructed via a biomimetic hetero-Diels–Alder reaction of a 2-azabutadiene. However, the presence of a hydroxyl group at C-3 (or C-5) of the pyridine ring, as in nosiheptide, presents a different challenge.[6] Therefore, as part of our ongoing work towards the synthesis of nosiheptide, we decided to investigate a complementary cycloaddition route to highly-functionalised pyridines, namely the hetero-Diels–Alder reaction of 1-aza-3-siloxy-1,3-butadienes with acetylenes.



lycodine omeprazole pyridine core of nosiheptide

Since the discovery by Ghosez and co-workers that *N*,*N*-dimethylhydrazones **1**, readily available from condensation of α,β-unsaturated aldehydes and *N*,*N*-dimethylhydrazine, participate readily in [4+2] cycloadditions,[7] the hetero-Diels–Alder reaction of 1-azabutadienes has proved to be a versatile method for the preparation of a large range of pyridines and dihydropyridines.[8–16] The high reactivity of these dienes towards electron deficient dienophiles has been attributed to the strong electron-donating effect of the dimethylamino substituent. Introduction of an additional electron-releasing substituent such as an alkyl (**1a**) or siloxy (**1b**) group into the C-3 position was also found to be beneficial.[9] In contrast, hetero-Diels–Alder reaction of analogous α,β-unsaturated oximes **2** have received relatively little attention in the literature.[17–23]



1a, R^1 = alkyl
1b, R^1 = $OSiR_3$

2

Keywords: Hetero-Diels–Alder reaction; Pyridines; Microwave irradiation.
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The scope of the hetero-Diels–Alder reaction of 1-azabutadienes has been extended by the discovery of Boger and Blagg that *N*-sulfonyl-2-(ethoxycarbonyl)-1-aza-1,3-butadienes participate in the [4+2] cycloadditions with electron rich dienophiles.[24] Fowler and co-workers have demonstrated that *N*-acyl-2-cyano-1-aza-1,3-butadienes may also be used.[25,26] In both cases cycloaddition takes place with inverse electron demand, in contrast to the hydrazones, which are considered as 'normal' electron rich dienes.

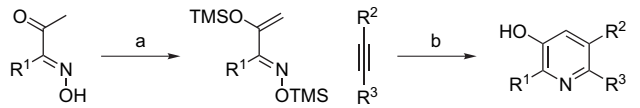
Herein we report our findings on the synthesis of highly-functionalised pyridines from 3-siloxy-1-aza-1,3-butadienes and electron deficient acetylenes. In particular, application of microwave irradiation has been investigated to decrease the relatively long reaction times commonly observed under standard thermal conditions. In accordance with Ghosez's initial observations, electron-donating substituents on nitrogen were found to accelerate the rate of cycloaddition.[9] Less electron rich dienes may also be employed, although higher temperatures and longer reaction times are often necessary.

2. Results and discussion

2.1. Synthesis and cycloadditions of α,β-unsaturated oximes

A range of 3-siloxy-1-azadienes **4a–d** was prepared from the corresponding free oximes **3a–d**[27–28] according to known or modified procedures,[17] and their reactivity in the hetero-Diels–Alder reaction was evaluated (Scheme 1). Furukawa and co-workers have reported that the cycloaddition of 1-azadiene **4a** and methyl ester **4b** with dimethyl acetylenedicarboxylate (DMAD, **5**) proceeds in 60% and 62% yield, respectively, after heating under reflux in benzene for 8 h.[17] However, attempts to repeat these results in our laboratory proved less successful, with the 3-hydroxypyridines **9a** and **9b** isolated in 38% and 42% yield, respectively, only after heating under reflux in benzene for several days (Table 1, entries 1 and 2). The trimethylsilyl group is presumably lost on work-up. Similar results were obtained on reaction of ester analogues **4c** and **4d** with DMAD (**5**) in refluxing toluene (Table 1, entries 3 and 4). Poor yields may be explained by the recovery of a large amount (up to 45%) of an *O*-trimethylsilyl keto-oxime side-product due to silyl enol ether hydrolysis under these conditions. As may be expected, changing the dienophile for the bulkier di-*tert*-butyl acetylenedicarboxylate (**6**) increases the reaction time and lowers the yield (Table 1, entry 5). Moderate yields were also obtained from the less reactive unsymmetrical dienophiles methyl propiolate (**7**, Table 1, entry 6) and 3-butyn-2-one (**8**, Table 1, entry 7). A single regioisomer was obtained in both cases, the regiochemistry being that expected on the basis of the likely coefficients of the relevant frontier orbitals ($HOMO_{diene}/LUMO_{dienophile}$).

The application of microwave irradiation has been shown to accelerate the rate of many organic reactions.[29,30] Indeed, several examples of hetero-Diels–Alder reactions have been reported under microwave conditions, including both 1- and 2-azadienes.[4,31–34] We envisaged that the long reaction times previously observed might be reduced by performing the reaction under these conditions. Unfortunately,



3a-d **4a-d** **5-8** **9a-d, 10-12**

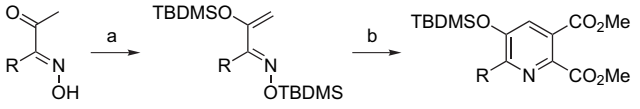
Scheme 1. **a**: R^1=Me, R^2=R^3=CO_2Me; **b**: R^1=R^2=R^3=CO_2Me; **c**: R^1=$CO_2{}^tBu$, R^2=R^3=CO_2Me; **d**: R^1=CO_2Bn, R^2=R^3=CO_2Me; reagents and conditions: (a) TMSCl, Et_3N, NaI, MeCN, rt, 18 h; (b) benzene or toluene, reflux, 4–14 days.

Table 1. Cycloaddition of α,β-unsaturated oximes with acetylenes under thermal conditions

Entry	R^1	R^2	R^3	Product	Time (days)	Yield (%)[a]
1	Me	CO_2Me	CO_2Me	**9a**	4	38
2	CO_2Me	CO_2Me	CO_2Me	**9b**	4	42
3	$CO_2{}^tBu$	CO_2Me	CO_2Me	**9c**	14	39
4	CO_2Bn	CO_2Me	CO_2Me	**9d**	6	48
5	CO_2Me	CO_2Me	$CO_2{}^tBu$	**10**	7	32
6[b]	CO_2Bn	H	CO_2Me	**11**	4	21
7[c]	CO_2Me	H	COMe	**12**	0.8	39

[a] Isolated yield after chromatography on silica.
[b] Methyl propiolate (2 equiv), toluene, sealed tube and 120 °C.
[c] 3-Butyn-2-one (5 equiv), toluene, sealed tube and 110 °C.

microwave irradiation of 1-azadiene **4b** with DMAD (**5**) in toluene in a sealed vessel at 150 °C afforded only degradation products. A more hydrolytically stable silyl protecting group was therefore investigated; we chose the bulkier *tert*-butyldimethylsilyl (TBDMS) derivatives **13a** and **13b**, prepared from the free oximes **3a** and **3b**, respectively, using TBDMS triflate and Hünigs base (Scheme 2). Treatment of **13a** and **13b** with either 1 or 2 equiv of DMAD (**5**) in a sealed tube at 150 °C under microwave irradiation (300 W) proceeded smoothly to afford the protected pyridines in moderate yields after only a few hours (Table 2, entries 1, 3 and 5). Increasing the temperature to 180 °C shortens the reaction time even further (Table 2, entries 2, 4, 6 and 7). A control



3a-b **13a-b** **14a-b**

Scheme 2. **a**: R=Me; **b**: R=CO_2Me; reagents and conditions: (a) TBDMSOTf, Et^iPr_2N, CH_2Cl_2, 0 °C, 5–18 h; (b) DMAD, toluene or toluene/THF, MW (300 W).

Table 2. Cycloaddition of α,β-unsaturated oximes with acetylenes under microwave conditions[a]

Entry	R	DMAD (equiv)	Temp (°C)	Time (h)	Product	Yield (%)[b]
1	Me	2.0	150	6	**14a**	56
2	Me	2.0	180	2	**14a**	56
3	Me	1.0	150	8	**14a**	50
4	Me	1.0	180	3	**14a**	50
5	CO_2Me	2.0	150	10	**14b**	32
6	CO_2Me	2.0	180	6	**14b**	31
7	CO_2Me	1.0	180	8	**14b**	45

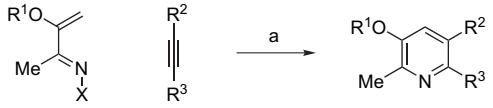
[a] Reactions were carried out in a CEM Discover™ microwave reactor operating at 300 W with simultaneous cooling.
[b] Isolated yield after chromatography on silica.

reaction performed in a sealed tube at 150 °C gave the appropriate pyridine **14a** in 57% yield after 6 h. However, the use of microwave irradiation remains as a safe, clean and efficient means for performing high temperature reactions and was used in the following studies on hydrazone derived 1-azadienes.

2.2. Synthesis and cycloadditions of α,β-unsaturated hydrazones

As discussed above, the most commonly used 1-azadienes in hetero-Diels–Alder reactions are the *N*,*N*-dimethylhydrazones **1a**, and a number of reactions with electron deficient alkenes and benzoquinones as dienophiles have been reported.[15] Reactions with alkynes are less common. The C-3 oxygenated 1-azadienes, hydrazones **1b**, are also known,[9,14,15,35] although to our knowledge, no Diels–Alder reactions of these dienes with alkynes have been reported. Hence, our initial work on hydrazones focussed on the cycloaddition of the previously unknown 1-dimethylamino-2-methyl-3-trimethylsiloxy-1-aza-1,3-butadiene with DMAD (**5**). However, only 30% of the desired cycloadduct was obtained after heating under reflux in toluene for 5 days. As has been shown with the oximes, a more hydrolytically stable diene is obtained by employing the TBDMS derivative. Thus, treatment of the known[35] 1-azadiene **17a** with DMAD (**5**) gave the desired cycloadduct **14a** in 53% yield after 20 h (Table 3, entry 3). Once again we turned our attention to the use of microwave irradiation in an attempt to decrease the reaction time and improve the yield.

Irradiation of equimolar amounts of 1-azadiene **17a** and DMAD (**5**) at 150 °C in toluene in a sealed tube for 2 h afforded the desired pyridine, still protected as the TBDMS ether and in poor yield, due to the competing formation of Michael adducts between the dienophile and liberated dimethylamine (Table 3, entry 4), a problem commonly observed with *N*,*N*-dimethylhydrazones that is not found with oximes.[14] Thus, 2 equiv of the dienophile were necessary to achieve complete consumption of the 1-azadiene, allowing the product to be isolated in comparable yield to the thermal reaction in only 2 h (Table 3, entry 5). Once again, increasing the temperature to 180 °C shortens the reaction time (Table 3, entry 6). A control reaction performed in a sealed tube at 150 °C under thermal conditions gave the appropriate pyridine **14a** in 46% yield after 2 h.



15-16, 17a-d **5, 7-8** **14a, 18-19**

Scheme 3. **a**: X=NMe_2, R^2=R^3=CO_2Me; **b**: X=piperidinyl, R^2=R^3=CO_2Me; **c**: X=NMeCbz, R^2=R^3=CO_2Me; **d**: X=phthalimido, R^2=R^3=CO_2Me; reagents and conditions: (a) toluene or toluene/THF, MW (300 W).

1-Azadienes **15** and **16** were prepared from butane-2,3-dione monohydrazone[35] via analogous procedures to the oximes in order to evaluate the effect of different silyl protecting groups on diene reactivity. Cycloaddition of triethylsilyl (TES) analogue **15** with DMAD (**5**) gave, after acidic work-up, the deprotected pyridine **9a** in 34% yield (Table 3, entry 1). The *tert*-butyldiphenylsilyl (TBDPS) analogue **16** however, could not be induced to undergo cycloaddition, even at elevated temperatures (Table 3, entry 2). This confirmed our choice of the TBDMS ether **17a** as the most suitable 3-siloxy-1-azadiene.

To date, the only comparative study on the effect of the N-1 nitrogen substituents of hydrazones on 1-azadiene reactivity has been reported by Gilchrist and co-workers.[36,37] Therefore, we prepared the 1-aza-1,3-butadienes **17b–d** from 2,3-butanedione in two steps by condensation with the appropriate hydrazine and silyl enol ether formation, in order to probe the effect on diene reactivity and reaction by-product profile. As expected, the piperidinyl derivative **17b** possessed similar reactivity to **17a** (Table 3, entry 7), including the formation of unwanted Michael adducts. Introduction of a single electron withdrawing substituent onto the leaving group (**17c**) also failed to prevent by-product formation (Table 3, entry 8). However, the introduction of a second electron withdrawing group in hydrazone **17d**, derived from *N*-aminophthalimide,[38] completely suppressed Michael addition of the nitrogen leaving group into the dienophile, leading to increased yield, although higher temperature is necessary to effect the cyclisation (Table 3, entry 9). Only a single equivalent of DMAD (**5**) is needed with this diene (Table 3, entry 10).

Table 3. Cycloaddition of α,β-unsaturated hydrazones with acetylenes under microwave conditions,[a] using 2 equiv of dienophile

Entry	1-Azadiene	R^1	R^2	R^3	Temp (°C)	Time (h)	Product	Yield (%)[b]
1	**15**	TES	CO_2Me	CO_2Me	150	2	**9a**	34
2	**16**	TBDPS	CO_2Me	CO_2Me	180	6	—	—
3[c]	**17a**	TBDMS	CO_2Me	CO_2Me	110	20	**14a**	53
4[d]	**17a**	TBDMS	CO_2Me	CO_2Me	150	2	**14a**	24
5	**17a**	TBDMS	CO_2Me	CO_2Me	150	2	**14a**	52
6	**17a**	TBDMS	CO_2Me	CO_2Me	180	0.75	**14a**	44
7	**17b**	TBDMS	CO_2Me	CO_2Me	150	2	**14a**	47
8	**17c**	TBDMS	CO_2Me	CO_2Me	150	4	**14a**	46
9	**17d**	TBDMS	CO_2Me	CO_2Me	180	3	**14a**	58
10[d]	**17d**	TBDMS	CO_2Me	CO_2Me	180	4	**14a**	54
11	**17a**	TBDMS	H	CO_2Me	180	6	**18**	29
12	**17a**	TBDMS	H	COMe	180	6	**19**	28

[a] Reactions were carried out in a CEM Discover™ microwave reactor operating at 300 W with simultaneous cooling.
[b] Isolated yield after chromatography on silica.
[c] Reaction carried out under thermal conditions in refluxing toluene.
[d] DMAD (1 equiv).

Unsymmetrical dienophiles **7** and **8** were also investigated. The most reactive 1-azadiene **17a** was chosen for this study as longer reaction times were expected with the less electron deficient (and hence less reactive) dienophiles. Indeed, increasing the reaction temperature to 180 °C for 6 h was necessary to achieve complete consumption of the diene. Poor yields of a single regioisomer were obtained, in an analogous fashion to the oximes (Table 3, entries 11and 12; Scheme 3).

3. Conclusions

The hetero-Diels–Alder reaction between 1-aza-3-siloxy-1,3-butadienes and electron deficient acetylenes has been investigated. We have expanded the scope of 3-siloxy-α,β-unsaturated oximes as heterodienes, and utilised microwave irradiation to reduce the often extended reaction times and improve the poor yields associated with this process.

A series of 3-siloxy-α,β-unsaturated hydrazones were also prepared and their reactivity in the hetero-Diels–Alder reaction was evaluated. More electron rich 1-azadienes proved to be most reactive, although side reactions were observed. Introduction of electron withdrawing groups into the hydrazone suppressed these side reactions, but higher temperatures were required for cycloaddition.

4. Experimental

Commercially available reagents were used throughout without further purification unless otherwise stated; solvents were dried by standard procedures. Light petroleum refers to the fraction with bp 40–60 °C and ether refers to diethyl ether. Reactions were routinely carried out under a nitrogen atmosphere. Microwave reactions were carried out in a CEM Discover™ 300 W focussed microwave reactor. Fully characterised compounds were chromatographically homogeneous. IR spectra were recorded in the range 4000–600 cm^{-1} using a Nicolet Magna FT-550 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 300 or 400 MHz (^{1}H frequencies, corresponding ^{13}C frequencies are recorded at 75 and 100 MHz). In the ^{13}C NMR spectra, signals corresponding to CH, CH_2 or CH_3 groups are assigned from DEPT. High and low-resolution mass spectra were recorded on a Micromass GCT time of flight high-resolution mass spectrometer, or at the EPSRC Mass Spectrometry Service (Swansea). Elemental analysis was carried out on a Perkin Elmer 2400 CHN analyser within ±0.3% of the theoretical values. Melting points were measured on a Gallenkamp electrothermal digital melting point apparatus or on a Reichert–Kofler hot stage apparatus. Compounds **3b**,[27] **3c**,[28] **3d**,[27] *N*,*N*-dimethyl butane-2,3-dione monohydrazone[35] and **17a**[35] were prepared according to literature procedure.

4.1. General procedure 1 for the silylation of α-keto-oximes

To a stirred mixture of the α-keto-oxime (13.5 mmol) and sodium iodide (2.02 g, 13.5 mmol) in dry acetonitrile (40 mL) was added dropwise triethylamine (5.46 g, 54.0 mmol) and chlorotrimethylsilane (5.87 g, 54.0 mmol). The mixture was stirred at room temperature overnight and then the solvent was removed in vacuo. Ether (60 mL) was added to the residue, which was then filtered. The filtrate was concentrated in vacuo and distilled (Kugelrohr) to afford the title compound.

4.2. General procedure 2 for the silylation of α-keto-oximes

To a stirred solution of the α-keto-oxime (5.0 mmol) in dry dichloromethane (10 mL) at 0 °C was added dropwise ethyldiisopropylamine (1.68 g, 13.0 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.30 g, 12.5 mmol). Stirring was continued at 0 °C for 2–4 h and then the solvent was evaporated. The residue was diluted with *n*-pentane (25 mL), stirred at 0 °C for 1 h, then filtered and evaporated to afford the title compound, which was used without further purification.

4.3. General procedure 3 for the preparation of α-keto-hydrazones

To a stirred solution of 2,3-butanedione (0.861 g, 10.0 mmol) in ethanol (10 mL) at 0 °C was added the hydrazine (11.0 mmol) in dropwise. Stirring was continued at 0 °C until the reaction was judged to be complete by TLC. The solution was then dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate–light petroleum (1:9) to afford the title compound.

4.4. General procedure 4 for the silylation of α-keto-hydrazones

To a stirred solution of the α-ketohydrazone (10.0 mmol) in dry dichloromethane (10 mL) at 0 °C was added dropwise ethyldiisopropylamine (1.68 g, 13.0 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.30 g, 12.5 mmol). Stirring was continued at 0 °C for 2 h and then the solvent was evaporated. The residue was diluted with *n*-pentane (25 mL), stirred at 0 °C for 1 h, then filtered and evaporated to afford the title compound, which was used without further purification.

4.5. General procedure 5 for hetero-Diels–Alder reaction under thermal conditions

Equimolar amounts of the 1-aza-1,3-butadiene and the dienophile were heated under reflux in the appropriate solvent (2 mL per mmol of 1-azadiene) for the time indicated. The resulting mixture was concentrated in vacuo, and the crude product was purified by flash chromatography on silica, eluting with methanol–chloroform (0.5:99.5–2:98) to afford the title compound.

4.6. General procedure 6 for hetero-Diels–Alder reaction under microwave irradiation

A solution of the 1-aza-1,3-butadiene (1.0 mmol) and the dienophile (1.0–2.0 mmol) in toluene (2 mL) in a sealed microwave tube (10 mL capacity) was irradiated at 300 W with simultaneous cooling and held at 150 °C for the time indicated. The resulting mixture was concentrated in vacuo,

and the crude product was purified by flash chromatography on silica, eluting with ethyl acetate–light petroleum (1:19) to afford the title compound.

4.7. General procedure 7 for hetero-Diels–Alder reaction under microwave irradiation

A solution of the 1-aza-1,3-butadiene (1.0 mmol) and the dienophile (1.0–2.0 mmol) in toluene (2 mL) and THF (0.25 mL) in a sealed microwave tube (10 mL capacity) was irradiated at 300 W with simultaneous cooling and held at 180 °C for the time indicated. The resulting mixture was concentrated in vacuo, and the crude product was purified by flash chromatography on silica, eluting with ethyl acetate–light petroleum (1:19) to afford the title compound.

4.7.1. 2-Methyl-1,3-bis(trimethylsiloxy)-1-aza-1,3-butadiene 4a. Following general procedure 1 using similar molar amounts, the title compound was obtained from 2,3-butanedione monoxime in 37% yield as a colourless oil, bp 80–100 °C (oven temperature) at 3 mmHg; δ_H (400 MHz, $CDCl_3$) 4.81 (1H, d, J=1.4 Hz, C=CH), 4.55 (1H, d, J=1.4 Hz, C=CH), 1.96 (3H, s, Me), 0.23 (9H, s, $SiMe_3$), 0.22 (9H, s, $SiMe_3$). This compound has been prepared previously.[17]

4.7.2. 2-Methoxycarbonyl-1,3-bis(trimethylsiloxy)-1-aza-1,3-butadiene 4b. Following general procedure 1 using similar molar amounts, the title compound was obtained from **3b** in 85% yield as a colourless oil, bp 130–150 °C (oven temperature) at 0.3 mmHg; δ_H (400 MHz, $CDCl_3$) 4.71 (1H, d, J=2.0 Hz, C=CH), 4.68 (1H, d, J=2.0 Hz, C=CH), 3.84 (3H, s, OMe), 0.22 (18H, s, 2×$SiMe_3$). This compound has been prepared previously.[17]

4.7.3. 2-*tert*-Butoxycarbonyl-1,3-bis(trimethylsiloxy)-1-aza-1,3-butadiene 4c. Following general procedure 1 using similar molar amounts, the *title compound* was obtained from **3c** in 82% yield as a colourless oil, bp 140–155 °C (oven temperature) at 0.3 mmHg; (Found: M^+, 331.1636. $C_{14}H_{29}NO_4Si_2$ requires 331.1636); ν_{max} (film)/cm^{-1} 2965, 1740, 1615, 1370, 1255, 1175, 1105, 1025, 965, 845, 755; δ_H (400 MHz, $CDCl_3$) 4.72 (1H, d, J=1.9 Hz, C=CH), 4.70 (1H, d, J=1.9 Hz, C=CH), 1.53 (9H, s, CMe_3), 0.23 (9H, s, $SiMe_3$), 0.22 (9H, s, $SiMe_3$); δ_C (100 MHz, $CDCl_3$) 162.6 (C), 155.5 (C), 148.6 (C), 100.7 (CH_2), 83.0 (CMe_3), 28.0 (CMe_3), 0.0 ($SiMe_3$), −0.9 ($SiMe_3$); m/z (EI) 331 (M^+, 17%), 275 (17), 274 (10), 259 (10), 147 (27), 115 (16), 113 (25), 75 (44), 74 (20), 73 (81), 57 (100).

4.7.4. 2-Benzyloxycarbonyl-1,3-bis(trimethylsiloxy)-1-aza-1,3-butadiene 4d. Following general procedure 1 using similar molar amounts, the *title compound* was obtained from **3d** in 66% yield as a colourless oil, bp 200–225 °C (oven temperature) at 0.3 mmHg; (Found: M^+, 365.1476. $C_{17}H_{27}NO_4Si_2$ requires 365.1479); ν_{max} (film)/cm^{-1} 3035, 2960, 2900, 1750, 1700, 1615, 1500, 1455, 1380, 1350, 1315, 1255, 1100, 1020; δ_H (300 MHz, $CDCl_3$) 7.42–7.30 (5H, m, ArH), 5.32 (2H, s, CH_2), 4.70 (1H, d, J=2.0 Hz, C=CH), 4.65 (1H, d, J=2.0 Hz, C=CH), 0.22 (9H, s, $SiMe_3$), 0.20 (9H, s, $SiMe_3$); δ_C (75 MHz, $CDCl_3$) 163.3 (C), 154.4 (C), 148.4 (C), 135.3 (C), 128.5 (CH), 128.3 (CH), 128.3 (CH), 101.1 (CH_2), 66.9 (CH_2), 0.0 ($SiMe_3$), −0.8 ($SiMe_3$); m/z (EI) 365 (M^+, 1%), 350 (2), 274 (19), 91 (100), 73 (56).

4.7.5. 2-Methyl-1,3-bis(*tert*-butyldimethylsiloxy)-1-aza-1,3-butadiene 13a. Following general procedure 2, the *title compound* (1.44 g, 87%) was obtained as a pale oil from 2,3-butanedione monoxime (0.435 g, 5.0 mmol); (Found: MH^+, 330.2281. $C_{16}H_{35}NO_2Si_2$+H requires 330.2284); ν_{max} (film)/cm^{-1} 2957, 2931, 2888, 2859, 1615, 1580, 1472, 1464, 1391, 1362, 1340, 1254, 1168; δ_H (300 MHz, $CDCl_3$) 4.78 (1H, d, J=1.1 Hz, C=CH), 4.48 (1H, d, J=1.1 Hz, C=CH), 1.96 (3H, s, Me), 0.94 (9H, s, CMe_3), 0.92 (9H, s, CMe_3), 0.16 (6H, s, $SiMe_2$), 0.14 (6H, s, $SiMe_2$); δ_C (75 MHz, $CDCl_3$) 158.2 (C), 154.1 (C), 96.6 (CH_2), 26.5 (Me), 26.1 (Me), 18.6 (CMe_3), 18.4 (CMe_3), 11.6 (Me), −4.1 ($SiMe_2$), −4.3 ($SiMe_2$); m/z (CI) 358 (15%), 330 (MH^+, 90), 314 (100), 272 (85), 231 (37), 216 (13), 200 (18), 189 (30), 156 (12), 115 (21).

4.7.6. 2-Methoxycarbonyl-1,3-bis(*tert*-butyldimethylsiloxy)-1-aza-1,3-butadiene 13b. Following general procedure 2, the *title compound* (1.73 g, 93%) was obtained as a pale oil from **3b** (0.716 g, 5.0 mmol); (Found: MH^+, 374.2182. $C_{17}H_{35}NO_4Si_2$+H requires 374.2183); ν_{max} (film)/cm^{-1} 2956, 2931, 2887, 2859, 1751, 1614, 1473, 1464, 1435, 1391, 1362, 1254, 1102; δ_H (300 MHz, $CDCl_3$) 4.68 (1H, d, J=2.1 Hz, C=CH), 4.64 (1H, d, J=2.1 Hz, C=CH), 3.83 (3H, s, OMe), 0.94 (9H, s, CMe_3), 0.89 (9H, s, CMe_3), 0.16 (12H, s, 2×$SiMe_2$); δ_C (75 MHz, $CDCl_3$) 164.3 (C), 155.2 (C), 149.1 (C), 100.3 (CH_2), 52.4 (Me), 26.1 (Me), 26.0 (Me), 18.5 (CMe_3), 18.3 (CMe_3), −4.3 ($SiMe_2$), −5.0 ($SiMe_2$); m/z (CI) 402 (8%), 374 (MH^+, 32), 358 (50), 316 (60), 286 (10), 247 (18), 231 (90), 200 (10), 189 (100), 184 (20), 157 (40), 147 (50), 115 (70), 86 (100), 73 (28).

4.7.7. 1-(Dimethylamino)-2-methyl-3-(trimethylsiloxy)-1-aza-1,3-butadiene. To a solution of *N*,*N*-dimethyl butane-2,3-dione monohydrazone (1.60 g, 12.5 mmol) and sodium iodide (0.934 g, 6.20 mmol) in acetonitrile (30 mL) was added triethylamine (2.52 g, 25.0 mmol) and chlorotrimethylsilane (2.71 g, 25.0 mmol). The reaction mixture was stirred for 18 h. The reaction mixture was then concentrated in vacuo and the residue was diluted with ether (50 mL), filtered under nitrogen and concentrated in vacuo. The crude product was distilled to afford the *title compound* as a brown oil (1.69 g, 68%), bp 115–130 °C (oven temperature) at 9 mmHg; (Found: M^+, 200.1343. $C_9H_{20}N_2OSi$ requires 200.1345); ν_{max} (film)/cm^{-1} 2990, 2955, 2900, 2860, 2820, 2775, 1685, 1615, 1590, 1470, 1440, 1335, 1280; δ_H (300 MHz, $CDCl_3$) 4.85 (1H, d, J=1.1 Hz, C=CH), 4.81 (1H, d, J=1.1 Hz, C=CH), 2.54 (6H, s, NMe_2), 2.02 (3H, s, Me), 0.22 (9H, s, $SiMe_3$); δ_C (75 MHz, $CDCl_3$) 159.5 (C), 155.3 (C), 96.8 (CH_2), 47.1 (Me), 14.2 (Me), 0.35 (Me); m/z (EI) 311 (25%), 271 (14), 200 (17), 185 (56), 151 (48), 135 (48), 109 (78), 86 (45), 73 (91), 58 (100).

4.7.8. 1-(Dimethylamino)-2-methyl-3-(triethylsiloxy)-1-aza-1,3-butadiene 15. To a solution of *N*,*N*-dimethyl butane-2,3-dione monohydrazone (1.28 g, 10.0 mmol) and sodium iodide (0.750 g, 5.00 mmol) in acetonitrile (20 mL) was added triethylamine (2.02 g, 20.0 mmol) and

chlorotriethylsilane (3.01 g, 20.0 mmol). The reaction mixture was stirred for 24 h, then further sodium iodide (0.375 g, 2.50 mmol), triethylamine (1.01 g, 10.0 mmol) and chlorotriethylsilane (1.50 g, 10.0 mmol) was added, and the reaction mixture was stirred for further 18 h. The reaction mixture was then concentrated in vacuo and the residue was diluted with ether (35 mL), filtered under nitrogen and concentrated in vacuo. The crude product was distilled in vacuo at room temperature to afford the *title compound* as a brown oil (1.62 g, 67%); (Found: M^+, 242.1808. $C_{12}H_{26}N_2OSi$ requires 242.1814); ν_{max} (film)/cm^{-1} 3428, 2953, 2821, 2777, 1684, 1611, 1589, 1459, 1415, 1379, 1337, 1238, 1210, 1147; δ_H (300 MHz, $CDCl_3$) 4.77 (1H, d, J=0.8 Hz, C═CH), 4.40 (1H, d, J=0.8 Hz, C═CH), 2.47 (6H, s, NMe_2), 1.97 (3H, s, Me), 0.93 (9H, t, J=7.9 Hz, 3×CH_2*Me*), 0.67 (6H, q, J=7.9 Hz, 3×CH_2Me); δ_C (75 MHz, $CDCl_3$) 160.2 (C), 155.9 (C), 96.0 (CH_2), 47.5 (Me), 14.6 (Me), 7.1 (Si(CH_2*Me*)$_3$), 7.0 (Si(CH_2*Me*)$_3$), 6.8 (Si(*C*H_2Me)$_3$), 5.6 (Si(*C*H_2Me)$_3$); *m*/*z* (EI) 242 (M^+, 18%), 227 (48), 217 (92), 213 (20), 189 (100), 170 (10), 161 (51), 133 (17), 115 (28), 105 (14), 87 (50), 83 (33), 75 (13), 58 (34).

4.7.9. 3-(*tert*-Butyldiphenylsiloxy)-1-(dimethylamino)-2-methyl-1-aza-1,3-butadiene 16. To a solution of *N*,*N*-dimethyl butane-2,3-dione monohydrazone (0.256 g, 2.00 mmol) and sodium iodide (0.150 g, 1.00 mmol) in acetonitrile (2 mL) was added triethylamine (0.405 g, 4.00 mmol) and *tert*-butyldiphenylsilyl chloride (1.10 g, 4.00 mmol). The reaction mixture was stirred for 3 days, then further sodium iodide (0.150 g, 1.00 mmol), triethylamine (0.405 g, 4.00 mmol) and *tert*-butyldiphenylsilyl chloride (1.10 g, 4.00 mmol) was added and stirring was continued for further 24 h. The reaction mixture was then concentrated in vacuo and the residue was diluted with ether (15 mL), cooled in an ice-bath for 30 min, filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica to afford the *title compound* as a brown oil (0.471 g, 64%); (Found: M^+, 366.2124. $C_{22}H_{30}N_2OSi$ requires 366.2127); ν_{max} ($CHCl_3$)/cm^{-1} 3392, 3072, 3050, 2958, 2931, 2892, 2858, 1611, 1590, 1472, 1428, 1336, 1317, 1157, 1114; δ_H (300 MHz, $CDCl_3$) 7.76–7.70 (4H, m, ArH), 7.42–7.34 (6H, m, ArH), 4.77 (1H, d, J=1.5 Hz, C═CH), 4.30 (1H, d, J=1.5 Hz, C═CH), 2.35 (6H, s, NMe_2), 2.06 (3H, s, Me), 1.05 (9H, s, CMe_3); δ_C (75 MHz, $CDCl_3$) 159.3 (C), 155.5 (C), 135.9 (CH), 135.4 (CH), 133.9 (C), 128.2 (CH), 96.8 (CH_2), 47.3 (NMe_2), 27.1 (Me), 20.2 (*C*Me_3), 14.9 (Me); *m*/*z* (EI) 366 (M^+, 19%), 351 (17), 309 (46), 273 (15), 266 (19), 200 (100), 181 (49), 135 (35), 77 (43).

4.7.10. 3-(Piperidin-1-ylimino)-butan-2-one. Following general procedure 3, the *title compound* (1.02 g, 62%) was obtained as a pale oil from 1-aminopiperidine (1.10 g, 11.0 mmol); (Found: MH^+, 169.1363. $C_9H_{16}N_2O$+H requires 169.1341); ν_{max} (film)/cm^{-1} 2939, 2856, 2822, 1687, 1581, 1443, 1354, 1294, 1261, 1156, 1119, 1103, 1074, 1014; δ_H (300 MHz, $CDCl_3$) 3.12–3.08 (4H, m, 2×CH_2), 2.35 (3H, s, Me), 1.98 (3H, s, Me), 1.74–1.67 (4H, m, 2×CH_2), 1.59–1.54 (2H, m, CH_2); δ_C (75 MHz, $CDCl_3$) 199.7 (C), 152.4 (C), 55.9 (CH_2), 25.7 (CH_2), 24.9 (Me), 24.4 (CH_2), 13.6 (Me); *m*/*z* (CI) 197 (8%), 169 (MH^+, 100), 84 (15).

4.7.11. 3-(*tert*-Butyldimethylsiloxy)-2-methyl-1-(piperidinyl)-1-aza-1,3-butadiene 17b. Following general procedure 4, the *title compound* (0.715 g, 84%) was obtained as a pale oil from 3-(piperidin-1-ylimino)-butan-2-one (0.504 g, 3.0 mmol); (Found: MH^+, 283.2205. $C_{15}H_{30}N_2O$-Si+H requires 283.2205); ν_{max} ($CHCl_3$)/cm^{-1} 3386, 2934, 2857, 2817, 1615, 1593, 1472, 1442, 1360, 1334, 1253, 1160, 1036; δ_H (300 MHz, $CDCl_3$) 4.86 (1H, d, J=0.9 Hz, C═CH), 4.52 (1H, d, J=0.9 Hz, C═CH), 2.75–2.71 (4H, m, 2×CH_2), 2.04 (3H, s, Me), 1.72–1.65 (4H, m, 2×CH_2), 1.48–1.44 (2H, m, CH_2), 0.96 (9H, s, CMe_3), 0.17 (6H, s, $SiMe_2$); δ_C (75 MHz, $CDCl_3$) 160.4 (C), 156.2 (C), 96.9 (CH_2), 56.5 (CH_2), 26.2 (CH_2), 25.7 (CH_2), 24.3 (CH_2), 18.8 (*C*Me_3), 14.8 (Me), −2.5 ($SiMe_2$); *m*/*z* 311 (8%), 283 (MH^+, 100), 267 (45), 225 (30), 200 (5), 169 (10), 159 (5).

4.7.12. 1-Benzyloxycarbonyl-1-methyl-hydrazine. To a stirred solution of methylhydrazine (0.461 g, 10.0 mmol) in dry dichloromethane (20 mL) at 0 °C was added triethylamine (1.21 g, 12.0 mmol) and benzyl chloroformate (1.88 g, 11.0 mmol). The reaction was allowed to warm to room temperature and stirred for 2 h. Water (15 mL) was added and the organic layer was separated. The aqueous layer was further extracted with dichloromethane (3×25 mL). The combined organics were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate–light petroleum (1:1) to afford the title compound as a pale oil (1.04 g, 58%), lit. bp 104–134 °C, 0.2 mmHg; ν_{max} ($CHCl_3$)/cm^{-1} 3026, 3014, 1697, 1627, 1498, 1455, 1395, 1351, 1310, 1230, 1169; δ_H (300 MHz, $CDCl_3$) 7.38–7.31 (5H, m, ArH), 5.15 (2H, s, CH_2), 3.82 (2H, br s, NH_2), 3.14 (3H, s, Me). This compound has been prepared previously.[39]

4.7.13. *N*-Benzyloxycarbonyl-*N*-methyl butane-2,3-dione monohydrazone. Following general procedure 3, the *title compound* (0.963 g, 78%) was obtained as a colourless solid from 1-methyl-1-benzyloxycarbonylhydrazine (0.991 g, 5.5 mmol), mp 64–65 °C (from light petroleum); (Found: MH^+, 249.1236. $C_{13}H_{16}N_2O_3$+H requires 249.1239); ν_{max} ($CHCl_3$)/cm^{-1} 3442, 3031, 2990, 2930, 1703, 1613, 1469, 1456, 1428, 1382, 1359, 1320, 1191, 1120; δ_H (300 MHz, $CDCl_3$) 7.39–7.32 (5H, m, ArH), 5.21 (2H, s, CH_2), 3.35 (3H, s, NMe), 2.44 (3H, s, Me), 1.95 (3H, s, Me); δ_C (75 MHz, $CDCl_3$) 199.2 (C), 164.8 (C), 153.6 (C), 136.3 (C), 129.0 (CH), 128.8 (CH), 128.5 (CH), 68.5 (CH_2), 39.3 (Me), 25.6 (Me), 14.6 (Me); *m*/*z* (CI) 339 (30%), 249 (MH^+, 100), 205 (25), 181 (10), 137 (10), 91 (48).

4.7.14. 1-(Benzyloxycarbonylmethylamino)-3-(*tert*-butyldimethylsiloxy)-2-methyl-1-aza-1,3-butadiene 17c. Following general procedure 4, the *title compound* (1.01 g, 93%) was obtained as a pale oil from *N*-benzyloxycarbonyl-*N*-methyl butane-2,3-dione monohydrazone (0.745 g, 3.0 mmol); (Found: MH^+, 363.2097. $C_{19}H_{30}N_2O_3$-Si+H requires 363.2104); ν_{max} ($CHCl_3$)/cm^{-1} 3024, 3016, 2958, 2932, 2887, 2859, 1698, 1595, 1472, 1427, 1389, 1336, 1256, 1228, 1168; δ_H (300 MHz, $CDCl_3$) 7.35–7.32 (5H, m, ArH), 5.15 (2H, s, CH_2), 5.04 (1H, d, J=1.3 Hz, C═CH), 4.60 (1H, d, J=1.3 Hz, C═CH), 3.20 (3H, s, NMe), 1.93 (3H, s, Me), 0.95 (9H, s, CMe_3), 0.16 (6H, s, $SiMe_2$); δ_C (75 MHz, $CDCl_3$) 178.0 (C), 163.5 (C), 154.7

(C), 136.8 (C), 128.9 (CH), 128.5 (CH), 128.4 (CH), 98.7 (CH_2), 67.9 (CH_2), 38.1 (Me), 26.1 (Me), 16.0 (CMe_3), 14.5 (Me), −2.5 ($SiMe_2$); *m/z* (CI) 453 (8%), 363 (MH^+, 25), 339 (8), 311 (10), 283 (80), 271 (22), 249 (12), 221 (20), 193 (57), 181 (25), 149 (27), 137 (18), 91 (100).

4.7.15. *N*-Phthaloyl butane-2,3-dione monohydrazone. To a stirred solution of 2,3-butanedione (8.61 g, 0.100 mol) in chloroform (200 mL) was added *N*-aminophthalimide (17.8 g, 0.110 mol). The reaction mixture was heated under reflux for 3 days, allowed to cool to room temperature, filtered and concentrated in vacuo to afford the title compound as a colourless solid (20.1 g, 87%), mp 157–158 °C (from chloroform), (lit.[38] mp 165 °C), which was used without further purification; δ_H (300 MHz, $CDCl_3$) 7.95–7.92 (2H, m, ArH), 7.82–7.79 (2H, m, ArH), 2.60 (3H, s, Me), 2.11 (3H, s, Me).

4.7.16. 3-(*tert*-Butyldimethylsiloxy)-2-methyl-1-(phthalimido)-1-aza-1,3-butadiene 17d. Following general procedure 4, the *title compound* (1.38 g, 79%) was obtained as a colourless solid from *N*-phthaloyl butane-2,3-dione monohydrazone (1.15 g, 5.0 mmol), mp 106–107 °C (from ethanol); (Found: MH^+, 345.1632. $C_{18}H_{24}N_2O_3Si$+H requires 345.1634); ν_{max} ($CHCl_3$)/cm^{-1} 2955, 2930, 2894, 2857, 1787, 1717, 1618, 1596, 1467, 1373, 1354, 1339, 1311, 1256, 1170, 1115; δ_H (300 MHz, $CDCl_3$) 7.89–7.86 (2H, m, ArH), 7.76–7.73 (2H, m, ArH), 5.30 (1H, d, *J*=1.3 Hz, C=CH), 4.75 (1H, d, *J*=1.3 Hz, C=CH), 2.07 (3H, s, Me), 1.00 (9H, s, CMe_3), 0.23 (6H, s, $SiMe_2$); δ_C (75 MHz, $CDCl_3$) 174.0 (C), 164.3 (C), 153.8 (C), 134.6 (CH), 131.6 (C), 124.0 (CH), 100.3 (CH_2), 26.1 (Me), 18.7 (CMe_3), 17.5 (Me), −4.7 ($SiMe_2$); *m/z* (CI) 373 (10%), 345 (MH^+, 95), 287 (50), 200 (32), 148 (100).

4.7.17. Dimethyl 5-hydroxy-6-methylpyridine-2,3-dicarboxylate 9a

(a) Following general procedure 5 from **4a** (0.466 g, 1.9 mmol) and DMAD (**5**, 0.270 g, 1.9 mmol) the title compound (0.162 g, 38%) was obtained after 4 days in toluene as yellow crystals, mp 163–166 °C (from ethyl acetate–light petroleum), (lit.[17] mp 157–159 °C); δ_H (300 MHz, $CDCl_3$) 9.50 (1H, br s, OH), 7.41 (1H, s, H-4), 3.90 (6H, s, 2×OMe), 2.54 (3H, s, Me); δ_C (75 MHz, $CDCl_3$) 166.9 (C), 166.4 (C), 153.2 (C), 150.5 (C), 138.7 (C), 127.6 (C), 121.3 (CH), 53.1 (2×Me), 18.8 (Me).

(b) Following general procedure 5 from 3-(trimethylsiloxy)-1-(dimethylamino)-2-methyl-1-aza-1,3-butadiene (0.721 g, 3.6 mmol) and DMAD (**5**, 0.512 g, 3.6 mmol) the title compound (0.246 g, 30%) was obtained after 5 days in toluene as yellow crystals; data as above.

(c) A solution of the 1-aza-1,3-butadiene **15** (0.242 g, 1.0 mmol) and DMAD (**5**, 0.284 g, 2.0 mmol) in toluene (2 mL) in a sealed microwave tube (10 mL capacity) was irradiated at 300 W with simultaneous cooling and held at 150 °C for 2 h. The resulting mixture was concentrated in vacuo. The residue was taken up in methanol (1 mL), 2 M HCl (1 mL) was added and the mixture was stirred for 5 min. The mixture was then neutralised with saturated $NaHCO_3$, extracted with ethyl acetate (3×15 mL) and the combined organics were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate–light petroleum (1:4) to afford the title compound as yellow crystals (0.076 g, 34%); data as above.

(d) To a stirred solution of **14a** (0.125 g, 0.401 mmol) in THF (4 mL) was added dropwise TBAF (1.0 M in THF, 1 mL, 1.00 mmol). Stirring was continued for 2 h, and the reaction was quenched with water (10 mL) and extracted with ethyl acetate (4×10 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate–light petroleum (1:1) to afford the title compound as a pale oil (0.064 g, 71%); data as above.

4.7.18. Dimethyl 5-(*tert*-butyldimethylsiloxy)-6-methylpyridine-2,3-dicarboxylate 14a

(a) Following general procedure 6 from **13a** (0.330 g, 1.0 mmol) and DMAD (**5**, 0.284 g, 2.0 mmol), the *title compound* (0.190 g, 56%) was obtained in 6 h as a pale oil; (Found: M^+, 339.1507. $C_{16}H_{25}NO_5Si$ requires 339.1502); ν_{max} (film)/cm^{-1} 2955, 2933, 2888, 2860, 1732, 1588, 1461, 1431, 1406, 1367, 1325, 1258, 1178, 1145, 1055, 1004; δ_H (300 MHz, $CDCl_3$) 7.35 (1H, s, H-4), 3.95 (3H, s, OMe), 3.90 (3H, s, OMe), 2.52 (3H, s, Me), 1.00 (9H, s, CMe_3), 0.25 (6H, s, $SiMe_2$); δ_C (75 MHz, $CDCl_3$) 167.1 (C), 166.5 (C), 155.0 (C), 151.8 (C), 142.0 (C), 126.4 (C), 125.0 (CH), 53.4 (Me), 53.3 (Me), 26.2 (Me), 20.5 (Me), 18.6 (CMe_3), −3.9 ($SiMe_2$); *m/z* (EI) 339 (M^+, 12%), 308 (8), 282 (36), 250 (100), 222 (18), 192 (28), 164 (20).

(b) Following general procedure 6 from **13a** (0.330 g, 1.0 mmol) and DMAD (**5**, 0.142 g, 1.0 mmol), the title compound (0.170 g, 50%) was obtained in 8 h as a pale oil; data as above.

(c) Following general procedure 7 from **13a** (0.330 g, 1.0 mmol) and DMAD (**5**, 0.284 g, 2.0 mmol), the title compound (0.190 g, 56%) was obtained in 2 h as a pale oil; data as above.

(d) Following general procedure 7 from **13a** (0.330 g, 1.0 mmol) and DMAD (**5**, 0.142 g, 1.0 mmol), the title compound (0.170 g, 50%) was obtained in 3 h as a pale oil; data as above.

(e) A solution of 1-azadiene **13a** (0.330 g, 1.0 mmol) and DMAD (**5**, 0.284 g, 2.0 mmol) in toluene (2 mL) in a sealed tube was heated to 150 °C for 6 h. The resulting mixture was concentrated in vacuo and the crude product was purified by flash chromatography on silica, eluting with ethyl acetate–light petroleum (1:19) to afford the title compound (0.194 g, 57%) as a pale oil; data as above.

(f) Following general procedure 6 from **17a** (0.242 g, 1.0 mmol) and DMAD (**5**, 0.284 g, 2.0 mmol), the title compound (0.176 g, 52%) was obtained in 2 h as a pale oil; data as above.

(g) Following general procedure 7 from **17a** (0.242 g, 1.0 mmol) and DMAD (**5**, 0.284 g, 2.0 mmol), the title compound (0.150 g, 44%) was obtained in 45 min as a pale oil; data as above.

(h) Following general procedure 6 from **17b** (0.283 g, 1.0 mmol) and DMAD (**5**, 0.284 g, 2.0 mmol), the title compound (0.160 g, 47%) was obtained in 2 h as a pale oil; data as above.
(i) Following general procedure 6 from **17c** (0.363 g, 1.0 mmol) and DMAD (**5**, 0.284 g, 2.0 mmol), the title compound (0.157 g, 46%) was obtained in 4 h as a pale oil; data as above.
(j) Following general procedure 7 from **17d** (0.344 g, 1.0 mmol) and DMAD (**5**, 0.284 g, 2.0 mmol), the title compound (0.197 g, 58%) was obtained in 3 h as a pale oil; data as above.
(k) Following general procedure 7 from **17d** (0.344 g, 1.0 mmol) and DMAD (**5**, 0.142 g, 1.0 mmol), the title compound (0.183 g, 54%) was obtained in 4 h as a pale oil; data as above.
(l) A solution of 1-azadiene **17a** (0.242 g, 1.0 mmol) and DMAD (**5**, 0.284 g, 2.0 mmol) in toluene (2 mL) in a sealed tube was heated to 150 °C for 2 h. The resulting mixture was concentrated in vacuo and the crude product was purified by flash chromatography on silica, eluting with ethyl acetate–light petroleum (1:19) to afford the title compound (0.157 g, 46%) as a pale oil; data as above.

4.7.19. Trimethyl 5-hydroxypyridine-2,3,6-tricarboxylate 9b. Following general procedure 5 from **4b** (0.839 g, 2.9 mmol) and DMAD (**5**, 0.412 g, 2.9 mmol) the title compound (0.327 g, 42%) was obtained after 4 days in benzene as yellow crystals, mp 121–124 °C (from ethanol), (lit.[17] mp 118–119 °C); δ_H (400 MHz, $CDCl_3$) 11.05 (1H, s, OH), 7.66 (1H, s, H-4), 4.06 (3H, s, OMe), 3.96 (3H, s, OMe), 3.95 (3H, s, OMe); δ_C (75 MHz, $CDCl_3$) 168.8 (C), 165.3 (C), 159.4 (C), 159.4 (C), 139.8 (C), 134.0 (C), 127.0 (CH), 54.7 (Me), 53.3 (Me), 53.2 (Me).

4.7.20. 6-*tert*-Butyl-2,3-dimethyl 5-hydroxypyridine-2,3,6-tricarboxylate 9c. Following general procedure 5 from **4c** (0.431 g, 1.3 mmol) and DMAD (**5**, 0.185 g, 1.3 mmol) the *title compound* (0.157 g, 39%) was obtained after 14 days in toluene as yellow crystals, mp 64–70 °C (from ether); (Found: C, 54.0; H, 5.47; N, 4.50. $C_{14}H_{17}NO_7$ requires C, 54.0; H, 5.50; N, 5.50%); (Found: M^+, 311.1013. $C_{14}H_{17}NO_7$ requires 311.1005); ν_{max} (film)/cm^{-1} 3300–2800, 1740, 1675, 1570, 1430, 1370, 1320, 1265, 1220, 1150, 1125, 1050, 970; δ_H (400 MHz, $CDCl_3$) 11.34 (1H, s, OH), 7.62 (1H, s, H-4), 3.94 (3H, s, OMe), 3.92 (3H, s, OMe), 1.66 (9H, s, CMe_3); δ_C (100 MHz, $CDCl_3$) 168.0 (C), 165.5 (C), 165.3 (C), 159.4 (C), 139.7 (C), 133.2 (C), 132.0 (C), 126.7 (CH), 85.6 (*C*Me_3), 53.1 (Me), 52.9 (Me), 28.0 (C*Me*$_3$); *m*/*z* (EI) 311 (M^+, 2%), 296 (5), 280 (10), 257 (19), 256 (74), 255 (35), 238 (34), 225 (22), 224 (81), 211 (10), 210 (63), 206 (48), 181 (14), 180 (26), 179 (85), 178 (29), 167 (17), 150 (15), 139 (32), 123 (18), 122 (10), 121 (36), 95 (11), 94 (17), 93 (22), 69 (16), 59 (39), 58 (14), 57 (100) 56 (48).

4.7.21. 6-Benzyl-2,3-dimethyl 5-hydroxypyridine-2,3,6-tricarboxylate 9d. Following general procedure 5 from **4d** (0.585 g, 1.6 mmol) and DMAD (**5**, 0.227 g, 1.6 mmol) the *title compound* (0.267 g, 48%) was obtained after 6 days in toluene as yellow crystals, mp 116–118 °C (from ethanol); (Found: C, 58.9; H, 4.21; N, 3.95. $C_{17}H_{15}NO_7$ requires C, 59.1; H, 4.38; N, 4.06%); (Found: M^+, 345.0850. $C_{17}H_{15}NO_7$ requires 345.0849); ν_{max} (Nujol)/cm^{-1} 3500–3100, 1735, 1725, 1685, 1560, 1460, 1430, 1345, 1315, 1265, 1200, 1150, 1130; δ_H (300 MHz, $CDCl_3$) 11.00 (1H, s, OH), 7.66 (1H, s, H-4), 7.49–7.30 (5H, m, ArH), 5.50 (2H, s, CH_2), 3.93 (3H, s, OMe), 3.92 (3H, s, OMe); δ_C (75 MHz, $CDCl_3$) 168.3 (C), 165.2 (C), 165.1 (C), 159.4 (C), 140.4 (C), 134.6 (C), 133.5 (C), 130.8 (C), 128.8 (CH), 128.7 (CH), 128.7 (CH), 127.0 (CH), 68.4 (CH_2), 53.2 (Me), 53.1 (Me); *m*/*z* (EI) 345 (M^+, 3%), 314 (17), 239 (70), 211 (89), 179 (3), 91 (100).

4.7.22. 2,3-Di-*tert*-butyl-6-methyl 5-hydroxypyridine-2,3,6-tricarboxylate 10. Following general procedure 5 from **4b** (0.811 g, 2.8 mmol) and DBAD (**6**, 0.634 g, 2.8 mmol) the *title compound* (0.320 g, 32%) was obtained after 7 days in toluene as yellow crystals, mp 119–122 °C (from ethanol); (Found: C, 57.7; H, 6.51; N, 3.87. $C_{17}H_{23}NO_7$ requires C, 57.8; H, 6.56; N, 3.96%); (Found: M^+, 353.1472. $C_{17}H_{23}NO_7$ requires 353.1475); ν_{max} (Nujol)/cm^{-1} 3230, 1735, 1685, 1560, 1455, 1370, 1315, 1200, 1145, 1120; δ_H (400 MHz, $CDCl_3$) 10.92 (1H, s, OH), 7.60 (1H, s, H-4), 4.05 (3H, s, OMe), 1.62 (9H, s, CMe_3), 1.60 (9H, s, CMe_3); δ_C (100 MHz, $CDCl_3$) 168.9 (C), 164.0 (C), 163.7 (C), 158.8 (C), 142.5 (C), 134.6 (C), 129.9 (C), 126.9 (H-4), 83.4 (*C*Me_3), 83.1 (*C*Me_3), 53.3 (Me), 27.9 (2×C*Me*$_3$); *m*/*z* (EI) 353 (M^+, 0.6%), 297 (1), 253 (5), 252 (5), 242 (65), 224 (56), 198 (44), 197 (21), 192 (13), 179 (10), 167 (21), 139 (34), 57 (100).

4.7.23. Trimethyl 5-(*tert*-butyldimethylsiloxy)pyridine-2,3,6-tricarboxylate 14b

(a) Following general procedure 6 from **13b** (0.374 g, 1.0 mmol) and DMAD (**5**, 0.284 g, 2.0 mmol), the *title compound* (0.121 g, 32%) was obtained in 10 h as a pale oil; (Found: M^+, 384.1473. $C_{17}H_{25}NO_7Si$+H requires 384.1478); ν_{max} ($CHCl_3$)/cm^{-1} 2955, 2934, 2888, 2862, 2254, 1742, 1589, 1555, 1430, 1409, 1363, 1336, 1253, 1215, 1170, 1148, 1119, 1047; δ_H (300 MHz, $CDCl_3$) 7.48 (1H, s, H-4), 3.92 (3H, s, OMe), 3.91 (3H, s, OMe), 3.90 (3H, s, OMe), 0.96 (9H, s, CMe_3), 0.25 (6H, s, $SiMe_2$); δ_C (75 MHz, $CDCl_3$) 165.9 (C), 165.7 (C), 164.7 (C), 152.7 (C), 144.0 (C), 141.4 (C), 131.3 (C), 128.7 (CH), 53.6 (Me), 53.5 (Me), 53.2 (Me), 25.7 (Me), 18.6 (*C*Me_3), −3.8 ($SiMe_2$); *m*/*z* (CI) 384 (MH^+, 6%), 270 (100), 238 (23).
(b) Following general procedure 7 from **13b** (0.374 g, 1.0 mmol) and DMAD (**5**, 0.284 g, 2.0 mmol), the title compound (0.119 g, 31%) was obtained in 6 h as a pale oil; data as above.
(c) Following general procedure 7 from **13b** (0.374 g, 1.0 mmol) and DMAD (**5**, 0.142 g, 1.0 mmol), the title compound (0.171 g, 45%) was obtained in 8 h as a pale oil; data as above.

4.7.24. 2-Benzyl-6-methyl 3-hydroxypyridine-2,6-dicarboxylate 11. A solution of 1-aza-1,3-butadiene **4d** (0.621 g, 1.7 mmol) and methyl propiolate (**7**, 0.294 g, 3.5 mmol) in toluene (2 mL) in a sealed tube was heated to 120 °C for 4 days. The resulting mixture was concentrated in vacuo and the crude product was purified by flash

chromatography on silica, eluting with methanol–chloroform (0.5:99.5–2:98) to afford the *title compound* (0.103 g, 21%) as yellow crystals, mp 102–106 °C (from ethanol); (Found: M^+, 287.0788. $C_{15}H_{13}NO_5$ requires 287.0794); ν_{max} (Nujol)/cm^{-1} 1725, 1665, 1595, 1580, 1430, 1425, 1350, 1310, 1220, 1180, 1135, 1095; δ_H (400 MHz, $CDCl_3$) 11.10 (1H, s, OH), 8.22 (1H, d, J=8.8 Hz, ArH), 7.52–7.47 (2H, m, ArH), 7.44 (1H, d, J=8.8 Hz, ArH), 7.41–7.31 (3H, m, ArH), 5.52 (2H, s, CH_2), 3.96 (3H, s, OMe); δ_C (100 MHz, $CDCl_3$) 169.0 (C), 164.6 (C), 161.0 (C), 139.8 (C), 134.8 (C), 131.0 (CH), 130.0 (C), 128.8 (CH), 128.7 (CH), 128.6 (CH), 126.7 (CH), 68.2 (CH_2), 52.8 (Me); *m/z* (EI) 287 (M^+, 0.4%), 256 (1), 181 (22), 153 (26), 92 (19), 91 (100), 65 (20), 57 (29), 55 (18).

4.7.25. Methyl 6-acetyl-3-hydroxypyridine-2-carboxylate 12. A solution 1-aza-1,3-butadiene **4b** (0.345 g, 1.19 mmol) and 3-butyn-2-one (**8**, 0.406 g, 5.96 mmol) in toluene (5 mL) in a sealed tube was heated to 110 °C for 20 h. The resulting mixture was concentrated in vacuo and the crude product was purified by flash chromatography on silica, eluting with ethyl acetate–light petroleum (1:3) to afford the *title compound* (0.090 g, 39%) as yellow crystals, mp 125–127 °C (from ethyl acetate–light petroleum); (Found: C, 55.1; H, 4.65; N, 7.18. $C_9H_9NO_4$ requires C, 55.4; H, 4.45; N, 7.04%); (Found: M^+, 195.0528. $C_9H_9NO_4$ requires 195.0532); ν_{max} (Nujol)/cm^{-1} 3120, 1700, 1685, 1655, 1575, 1560, 1540, 1290, 1275, 1210, 1175, 1130, 1105, 1090; δ_H (300 MHz, $CDCl_3$) 11.08 (1H, s, OH), 8.15 (1H, d, J=8.8 Hz, ArH), 7.40 (1H, d, J=8.8 Hz, ArH), 4.05 (3H, s, OMe), 2.67 (3H, s, COMe); δ_C (100 MHz, $CDCl_3$) 198.2 (C), 169.6 (C), 161.3 (C), 145.9 (C), 128.6 (C), 127.9 (CH), 126.6 (CH), 53.3 (Me), 25.2 (Me); *m/z* (EI) 195 (M^+, 100%), 180 (16), 167 (13), 153 (24), 152 (50), 137 (56), 136 (17), 135 (28), 122 (23), 121 (68), 120 (22), 107 (31), 94 (17), 93 (19), 64 (15), 59 (19), 53 (15).

4.7.26. Methyl 3-(*tert*-butyldimethylsiloxy)-2-methylpyridine-6-carboxylate 18. Following general procedure 7 from **17a** (0.242 g, 1.0 mmol) and methyl propiolate (**7**, 0.168 g, 2.0 mmol), the *title compound* (0.082 g, 29%) was obtained in 6 h as a pale oil; (Found: M^+, 282.1526. $C_{14}H_{23}NO_3Si$ requires 282.1525); ν_{max} (film)/cm^{-1} 2956, 2934, 2887, 2861, 2254, 2235, 1719, 1574, 1463, 1408, 1392, 1364, 1325, 1258, 1199, 1120, 1007; δ_H (300 MHz, $CDCl_3$) 7.88 (1H, d, J=8.3 Hz, ArH), 7.06 (1H, d, J=8.3 Hz, ArH), 3.92 (3H, s, OMe), 3.51 (3H, s, Me), 0.98 (9H, s, CMe_3), 0.22 (6H, s, $SiMe_2$); δ_C (75 MHz, $CDCl_3$) 168.3 (C), 156.0 (C), 154.4 (C), 142.1 (C), 127.2 (CH), 127.0 (CH), 55.5 (Me), 28.2 (Me), 22.8 (Me), 20.8 (CMe_3), −1.3 ($SiMe_2$); *m/z* (CI) 282 (M^+, 100%).

4.7.27. 6-Acetyl-3-(*tert*-butyldimethylsiloxy)-2-methylpyridine 19. Following general procedure 7 from **17a** (0.242 g, 1.0 mmol) and 3-butyn-2-one (**8**, 0.136 g, 2.0 mmol), the *title compound* (0.073 g, 28%) was obtained in 6 h as a pale oil; (Found: M^+, 339.1507. $C_{14}H_{23}NO_3Si$ requires 339.1502); ν_{max} ($CHCl_3$)/cm^{-1} 2933, 2959, 2887, 2861, 2252, 1684, 1643, 1596, 1569, 1508, 1460, 1392, 1359, 1309, 1256, 1211, 1181, 1117, 1006; δ_H (300 MHz, $CDCl_3$) 7.83 (1H, d, J=8.3 Hz, ArH), 7.07 (1H, d, J=8.3 Hz, ArH), 2.66 (3H, s, Me), 2.49 (3H, s, Me), 1.02 (9H, s, CMe_3), 0.25 (6H, s, $SiMe_2$); δ_C (75 MHz, $CDCl_3$) 199.9 (C), 153.8 (C), 150.7 (C), 146.6 (C), 124.7 (CH), 121.5 (CH), 26.0 (Me), 20.5 (Me), 18.6 (CMe_3), −3.5 ($SiMe_2$); *m/z* (CI) 266 (MH^+, 100%), 152 (5).

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