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Tandem oxidation processes for the regioselective preparation of 5-substituted and 6-substituted 1,2,4-triazines

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Abstract—α-Hydroxyketones undergo MnO_2-mediated oxidation, followed by in situ trapping with 2-pyridylamidrazone, to give 3-pyridyl-5-substituted 1,2,4-triazines in a one-pot procedure, which avoids the need to isolate the reactive α-ketoaldehyde intermediates. By modifying this procedure to allow condensation prior to oxidation, the corresponding 6-substituted 1,2,4-triazines were obtained. The preparation of a novel unsymmetrical 2,2′-bipyridine using one of the pyridyl 1,2,4-triazines prepared herein is also described.

1,2,4-Triazines are an important class of nitrogen-containing heterocycles with diverse applications in medicine and agrochemistry and as ligands for a range of metal ions.[1,2] In addition, 1,2,4-triazines are versatile synthetic building blocks from which a wide-range of heterocyclic systems can be accessed via an inverse-electron-demand Diels–Alder sequence.[3–6] The use of this methodology to prepare pyridines is particularly valuable,[3–5] and we have recently reported[5] a microwave (MW) variant of the Boger enamine procedure,[4a] which allows the direct conversion of substituted 1,2,4-triazines into highly functionalised pyridines and 2,2′-bipyridines via an inverse-electron-demand enamine Diels–Alder/retro-Diels–Alder/elimination sequence[5] (Scheme 1). We have also shown that substituted triazines can undergo a one-pot cascade process involving inverse-electron-demand Diels–Alder/retro-Diels–Alder/intramolecular-Diels–Alder reactions producing diaza-polycycles[6] (Scheme 1).

We next wished to apply the former procedure to prepare a range of novel, unsymmetrical 2,2′-bipyridines, but in order to do this we required efficient access to pyridyl-substituted triazines **1** and **2**. Of the many methods available to prepare triazines,[1] the double condensation of 1,2-dicarbonyl compounds with amidrazones developed by Neunhoeffer is one of the most straightforward. In this procedure, regio-isomeric mixtures are often formed from unsymmetrical diketones, although α-ketoaldehydes **4** normally give 5-substituted 1,2,4-triazines.[1] However, the high reactivity of α-ketoaldehydes, especially alkyl-substituted examples,[7] can present difficulties. We have recently shown that manganese dioxide-based tandem oxidation processes (TOPs) can be employed with α-ketoalcohols; for example, in the presence of diamines, the intermediate α-ketoaldehydes can be trapped to give heterocyclic systems.[8] The first objective of the present study, therefore, was to investigate the direct conversion of α-hydroxyketones **3** into 3-pyridyl-5-substituted triazines **1** by in situ trapping of the intermediate α-ketoaldehydes **4** with the pyridyl-substituted amidrazone **5**[9] (Scheme 2).

Preliminary studies were carried out using the commercially available α-hydroxyacetophenone **3a** (R = Ph) with 2-pyridylamidrazone **5** in the presence of activated manganese dioxide (Table 1). Initially, thermal conditions were employed with added 4 Å molecular sieves but the results were disappointing (entries i and ii). With excess manganese dioxide, as is normally employed, the reaction was slow (72 h) and triazine **1a** was obtained in only 9% isolated yield (contaminated by **2a**, R = Ph; **1a**:**2a** ca. 19:1). It appeared that amidrazone **5** was undergoing oxidative decomposition under these conditions and so the amount of MnO_2 was decreased to one equivalent: this change increased the yield of **1a** to 27%,

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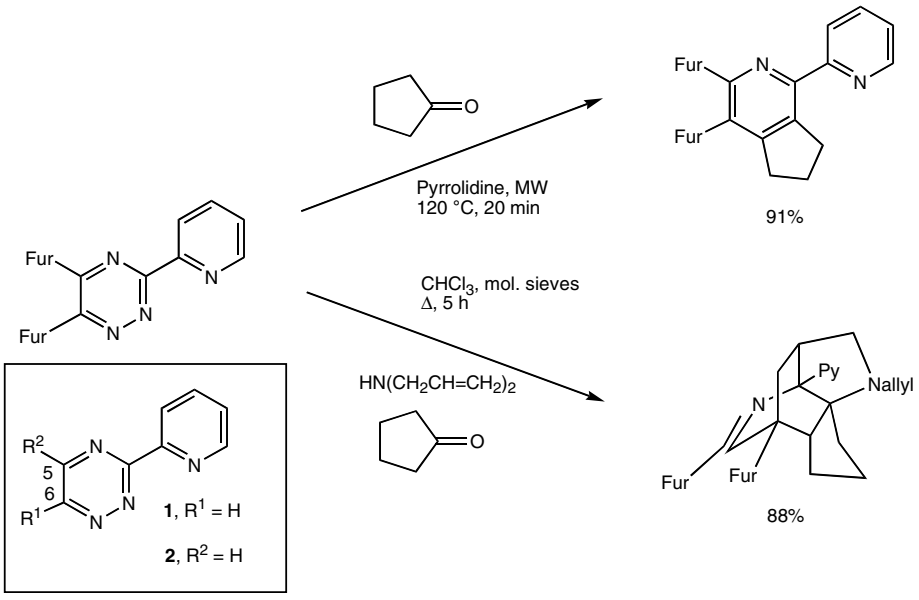
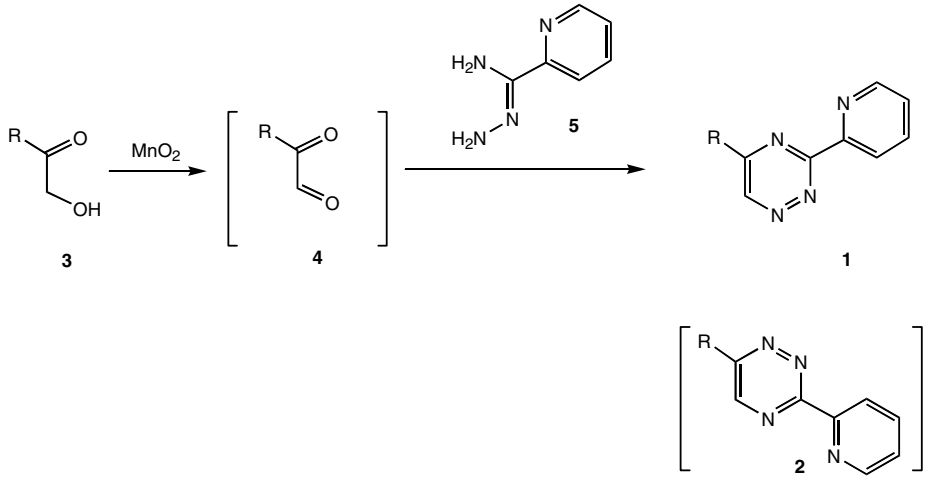
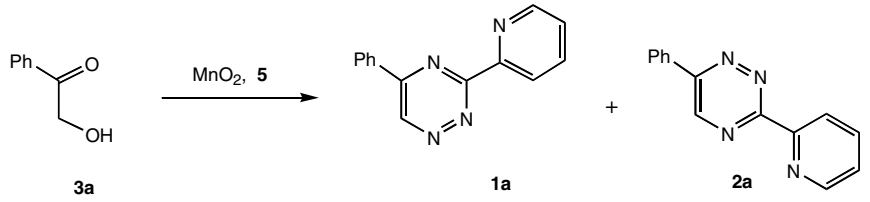


Scheme 1.



Scheme 2.

Table 1. Optimisation of the oxidation-trapping reaction of **3a** to give triazine **1a**



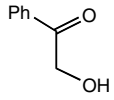
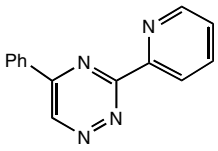
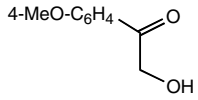
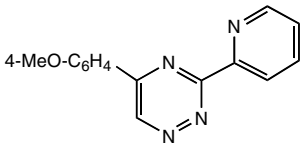
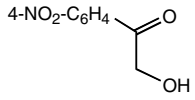
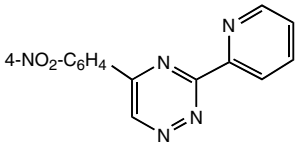
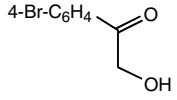
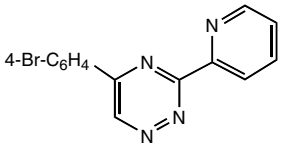
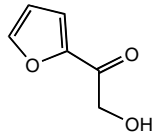
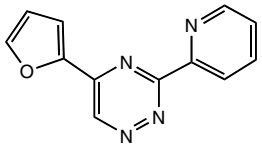
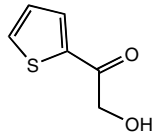
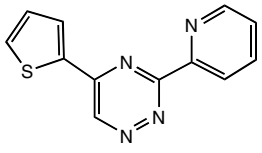
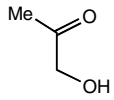
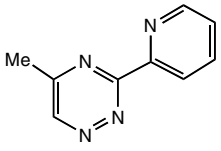
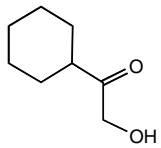
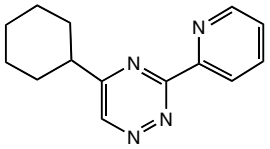
Entry	Equiv MnO_2	Conditions	Time	Isolated yield (%)	Ratio[a] **1a**:**2a**
i	9	CH_2Cl_2, reflux, 4 Å mol. sieves	72 h	9	19:1
ii	1	CH_2Cl_2, reflux, 4 Å mol. sieves	72 h	27[b]	19:1
iii	2	CH_2Cl_2, 55 °C, MW[c]	30 min	55	19:1
iv	**1**	**CH_2Cl_2, 55 °C, MW[c]**	**30 min**	**70**	**19:1**
v	1	CH_2Cl_2, 55 °C, MW[c]	15 min	60	19:1
vi	**1**	**PhMe, 55 °C, MW[c]**	**30 min**	**70**	**19:1**

[a] Determined by ^1H NMR spectroscopy.
[b] **3a** (26%) recovered; 65% recovered after 24 h.
[c] CEM Discover microwave reactor.

although unreacted starting material and non-cyclised hydrazone intermediates were also obtained. In order to speed up the oxidation-trapping process (and minimise amidrazone degradation), we moved on to study the microwave-induced process (Table 1, entries iii–vi). We were delighted to find that on repeating the reaction using dichloromethane and 2 equiv of MnO_2 in a focused monomode microwave reactor at a fixed temperature (55 °C) in a sealed vessel, the reaction was complete in 30 min and adduct **1a** was isolated in 55% yield (entry iii). Using the same conditions but with 1 equiv of MnO_2 the yield improved to 70% (entry iv); changing the reaction time to 15 min resulted in a lower yield (entry v) but replacing dichloromethane with toluene also gave a 70% yield in 30 min (entry vi).

With this success in hand, we went on to look at a range of α-hydroxyketones **3a**–**h**[10] (Table 2). As can be seen, this one-pot process proved successful with a number of aromatic and heteroaromatic systems, the products

Table 2. One-pot preparation of 3-pyridyl-5-substituted-1,2,4-triazines **1a**–**h**[a]

Entry	α-Hydroxy ketone **3**		Triazine **1**		Yield[b] (%)
i		**3a**		**1a**	70[c]
ii		**3b**		**1b**	51
iii		**3c**		**1c**	76[11,12]
iv		**3d**		**1d**	59[d]
v		**3e**		**1e**	65
vi		**3f**		**1f**	69
vii		**3g**		**1g**	19[e]
viii		**3h**		**1h**	18[f]

[a] For a representative procedure see Ref. 11.
[b] Isolated yield based on the starting α-hydroxyketone **3**.
[c] **1a**:**2a** approx. 19:1.
[d] **1d**:**2d** approx. 19:1.
[e] Hydrazone **6** (35%) was also isolated (see Scheme 3).
[f] **1h**:**2h** approx. 4:1.

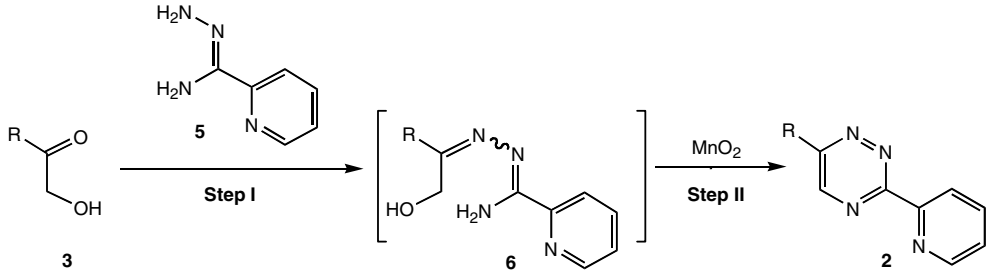
1a–**f** being obtained in fair to good yields (51–76%), predominantly or exclusively as the required regioisomers (entries i–vi).

Two aliphatic examples were also explored (entries vii–viii): in these examples low yields of triazines **1g** and **1h** were obtained. In the case of the methyl substituted example (entry vii), 35% of the hydrazone by-product **6** (R = Me) was also isolated, indicating the competitive nature of the condensation process in this system.

This observation prompted us to investigate the one-pot preparation of 3-pyridyl-6-substituted triazines **2** by an initial condensation between hydroxyketone **3** and amidrazone **5**, giving intermediate adduct **6**, followed in situ by MnO_2-mediated oxidation and subsequent condensation to produce the required product **2** (Scheme 3).

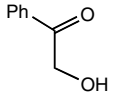
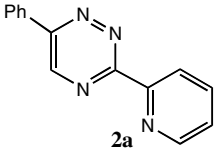
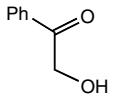
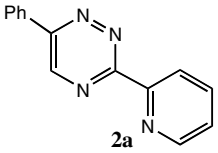
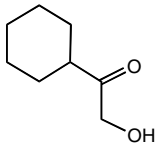
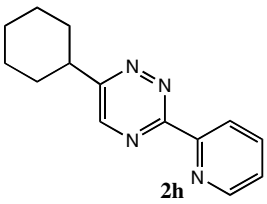
Preliminary studies revealed that this approach shows great potential (Table 3). Thus (entry i), condensation of α-hydroxyacetophenone **3a** with 2-pyridylamidrazone **5** followed by manganese dioxide oxidation–cyclisation in refluxing toluene,[14] gave 3-pyridyl-6-phenyl 1,2,4-triazine **2a** in 73% yield, although it was contaminated by a small amount of the 5-phenyl isomer **1a** (ca. 5%). Somewhat surprisingly, it appears that this 5-phenyl by-product arises from the aerial oxidation of α-hydroxyacetophenone **3a**, followed by condensation with the resulting aldehyde **4a**. However, by rigorously degassing the reaction mixture and carrying out the process under an inert atmosphere, the sequence proceeded with total regioselectivity according to ^{1}H NMR spectroscopy (entry ii). This sequence was then applied to the cyclohexane-substituted α-hydroxyketone **3h**, and triazine **2h** was obtained as a single regioisomer in 51% yield (73% using MW). Further studies are needed to examine the scope of this procedure, but these preliminary results, which involve both an aromatic and an aliphatic α-hydroxyketone, indicate its potential.

Finally, to illustrate the value of the 1,2,4-triazines prepared herein, 3-pyridyl-6-phenyl 1,2,4-triazine **2a** was converted into the novel, unsymmetrical 2,2′-bipyridine **7**[15] using the one-pot methodology we developed earlier[5] (Scheme 4).

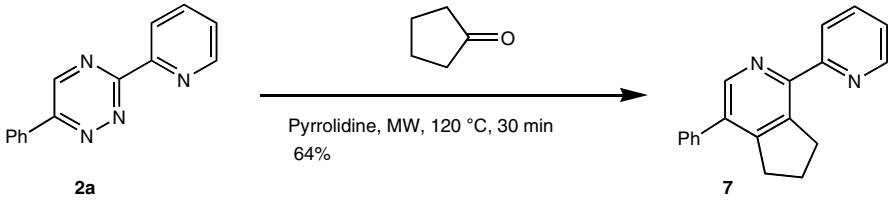


Scheme 3.

Table 3. One-pot preparation of 3-pyridyl-6-substituted 1,2,4-triazines **2a** and **2h**[a]

Entry		Step I (condensation)	Step II (oxidation, etc.)	Product **2**	Overall yield[b] (%)
i	 **3a**	**5** (2.0 equiv), PhMe, 55 °C, 1 h	MnO_2, PhMe, reflux, 17 h	 **2a**	73 (**2a**:**1a** = 19:1)
ii	 **3a**	**5** (2.0 equiv), PhMe, 55 °C, 1 h, degassed	MnO_2, PhMe, reflux, 17 h	 **2a**	71 (**2a** only)
iii	 **3h**	**5** (1.0 equiv), PhMe, 55 °C, 2 h, degassed	MnO_2, AcOH, PhMe, reflux, 17 h	 **2h**	51[13] (73)[c]

[a] For a representative procedure see Ref. 13.
[b] Isolated yield over complete sequence based on the starting α-hydroxyketone **3**.
[c] Using microwave conditions (2 h).



Scheme 4.

In summary, we have developed improved procedures for the regioselective conversion of α-hydroxyketones **3** into both 5-substituted- and 6-substituted-3-pyridyl 1,2,4-triazines via one-pot oxidative sequences with in situ trapping using 2-pyridylamidrazone (and presumably other substituted amidrazones would be equally viable). A novel, unsymmetrical 2,2′-bipyridine has also been prepared. We are currently optimising this chemistry and exploring applications in natural product synthesis.

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10. Non-commercial α-hydroxyketones were prepared from the corresponding methyl ketones using a published procedure: Moriarty, R. M.; Berglund, B. A.; Penmasta, R. *Tetrahedron Lett.* **1992**, *33*, 6065–6068.
11. Representative procedure: 5-(4-nitrophenyl)-3-(pyridin-2-yl) 1,2,4-triazine **1c**: In a sealed 10 mL CEM Discover® reaction vial containing a magnetic follower was placed 2-hydroxy-1-(4-nitrophenyl)ethanone **3c** (54 mg, 0.3 mmol), 2-pyridylamidrazone **5** (41 mg, 0.3 mmol), activated manganese dioxide (Aldrich 21,764-6, 31 mg, 0.3 mmol) and CH_2Cl_2 (0.5 mL). The reaction mixture was irradiated at 55 °C for 30 min (maximum power, 50 W; maximum pressure, 300 psi; run time, 10 min; stirring on; cooling off). The reaction mixture was cooled to rt, diluted with CH_2Cl_2 (5 mL), filtered through Celite® and concentrated in vacuo to furnish a yellow solid (65 mg). This was purified by flash column chromatography on silica gel (EtOAc) to give the title compound **1c** (64 mg, 76%) as a bright yellow solid, R_f 0.28 (EtOAc), mp 256–258 °C (lit.[12] 246–248 °C), which displayed consistent ^{1}H NMR data.
12. Culbertson, B. M.; Parr, G. R. *J. Heterocycl. Chem.* **1967**, *4*, 422–424.
13. Representative procedure: 6-(cyclohexyl)-3-(pyridin-2-yl) 1,2,4-triazine **2h**: 1-Cyclohexyl-2-hydroxyethanone **3h** (93 mg, 0.65 mmol), 2-pyridylamidrazone **5** (89 mg, 0.65 mmol) and dry, degassed PhMe (1.0 mL) were stirred at rt for 3 h under an atmosphere of argon. Analysis by TLC indicated complete consumption of hydroxyketone **3h**. After adding activated manganese dioxide (Aldrich 21,764-6, 0.665 g, 6.50 mmol), glacial acetic acid (0.037 mL, 0.59 mmol) and PhMe (7.0 mL), the reaction mixture was heated to reflux for 17 h. The reaction mixture was cooled to rt, diluted with CH_2Cl_2 (5.0 mL) and filtered through a pad of Celite®, covered by sodium hydrogencarbonate (1.0 g) and magnesium sulfate. The filtrate was concentrated in vacuo to furnish a brown oil (185 mg), which was purified by flash column chromatography on silica gel (EtOAc) to give the title compound **2h** (80 mg, 51%) as a pale yellow solid: R_f 0.16 (EtOAc); mp 110–111 °C; ν_{max} (film)/cm^{-1} 2926, 1586; δ_H (400 MHz, $CDCl_3$) 8.81 (1H, ddd, *J* 4.5, 1.5, 1.0), 8.63 (1H, s), 8.61

(1H, ddd (appt dt), *J* 7.5, 1.0), 7.85 (1H, ddd (appt td), *J* 7.5, 1.5), 7.40 (1H, ddd, *J* 7.5, 4.5, 1.0), 3.01–2.93 (1H, m), 1.98–2.02 (2H, m), 1.84–1.89 (2H, m), 1.73–1.76 (1H, m), 1.59–1.69 (2H, m), 1.35–1.47 (2H, m) 1.21–1.33 (1H, m); δ_C (100 MHz, $CDCl_3$) 164.7, 162.0, 152.9, 150.5, 149.0, 137.3, 125.5, 123.7, 42.1, 31.7, 25.7, 25.2; *m*/*z* (CI) 241 (MH^+, 100) [HRMS (CI): calcd for $C_{14}H_{17}N_4$, 241.1453. Found: MH^+, 241.1446 (3.5 ppm error)].

14. Microwaves could also be employed for the second step (PhMe, 120 °C, 1 h), although the initial condensation proceeded more efficiently under thermal conditions.
15. Representative procedure: 4-phenyl-1-(pyridin-2-yl)-6,7-dihydro-5*H*[2]pyrindine **7**: To a 10 mL CEM Discover® reaction vial, containing a magnetic follower, was placed 6-phenyl-3-pyridin-2-yl-1,2,4-triazine **2a** (0.023 g, 0.1 mmol), pyrrolidine (0.009 mL, 0.1 mmol) and cyclopentanone (0.009 mL, 0.1 mmol). The reaction mixture was irradiated at 120 °C for 30 min (maximum power, 300 W; maximum pressure, 300 psi; run time, 15 min; stirring on; cooling off). The reaction mixture was cooled to rt and diluted with CH_2Cl_2 (1 mL). Concentration in vacuo and purification by flash chromatography on silica gel (petroleum ether–ethyl acetate, 1:1) gave **7** (0.017 g, 64%) as a yellow solid: R_f 0.25 (petrol–EtOAc, 4:1); mp 121–122 °C (hexane–$CHCl_3$); ν_{max} (film)/cm^{-1} 2956, 1583; δ_H (400 MHz, $CDCl_3$) 8.72 (1H, ddd, *J* 4.8, 2.0, 0.8), 8.56 (1H, s), 8.20 (1H, ddd (appt dt), *J* 7.6, 1.2), 7.83 (1H, ddd (appt dt), *J* 7.6, 2.0), 7.54–7.38 (5H, m), 7.29 (1H, ddd, *J* 7.6, 4.8, 1.2), 3.45 (2H, t, *J* 7.6), 3.05 (2H, t, *J* 7.6), 2.10 (2H, quint, *J* 7.6); δ_C (100 MHz, $CDCl_3$) 157.98, 153.38, 150.65, 148.71, 146.52, 139.34, 137.70, 136.41, 133.67, 128.59, 128.54, 127.70, 123.01, 122.72, 33.35, 32.63, 25.50; *m*/*z* (CI): 273 (MH^+, 100%) [HRMS (CI): calcd for $C_{19}H_{17}N_2$, 273.1392. Found: MH^+, 273.1393 (−0.6 ppm error)].