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A new multicomponent reaction for the synthesis of pyridines via cycloaddition of azadienes and ketenimines

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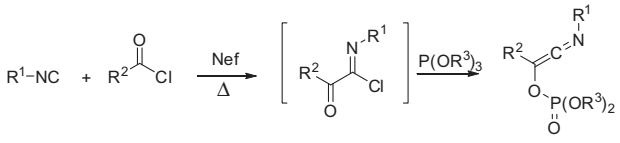
ABSTRACT

The ketenimines resulting from a Nef isocyanide/Perkow sequence react with 1-azadienes to form pyridines or pyrimidines depending on their substitution pattern. The reaction is most efficient with ester-substituted ketenimines which leads to pyridines after elimination of the phosphate group.

Most medicinal compounds are small synthetic organic molecules, many of which contain heterocyclic rings. In addition, the most potent ligand systems in (transition) metal mediated (asymmetric) catalysis are based on heterocyclic cores. However, the range of easily accessible and suitably functionalized heterocyclic building blocks is still surprisingly limited and the construction of even a small array of relevant heterocyclic compounds is often far from trivial. Heterocyclic chemistry, therefore, continues to attract the attention of the chemistry community and the development of novel methodologies to access heterocycles efficiently is highly appreciated.[1] In this context, methodology based on multicomponent reactions (MCRs) has received growing attention.[2] Starting from three or more simple building blocks, complex (hetero)cyclic scaffolds can be constructed in a single operation. Relatively unexplored building blocks in MCR chemistry are ketenimines, which were first reported in 1919.[3] Besides their use as dehydrating agents, they have found many applications in the synthesis of heterocycles by condensation with polar π bonds.[4] Following our ongoing interest in isocyanide-based MCRs, we recently disclosed a new solvent-free preparation of ketenimines from isocyanides.[5] This synthesis features a Nef coupling[6] of an isocyanide and an acid chloride followed by trapping the resulting imidoyl chloride by a phosphite (Scheme 1).

The resulting ketenimines are functionalized with a phosphate moiety, which should have a strong influence on the reactivity of these species. In cycloaddition reactions, the presence of the phosphate group could direct reactions with either the alkene or the imine moiety. We have already explored the reactivity of these intermediates toward several 1,3-dipoles.[7] Taking into account our interest in multicomponent reactions, we decided to further examine these regio-selectivity issues using 1-azadienes as the 'diene'. In earlier work, we showed that 1-azadienes are versatile intermediates, formed via a one-pot reaction of phosphonates, nitriles, and aldehydes, which may be trapped in situ by a fourth component (isocyanates, isothiocyanate, isocyanoesters) to obtain complex heterocycles with high functional diversity (Scheme 2).[8] When ketenimines are reacted with the in situ formed 1-azadienes, pyridine or pyrimidine derivatives may be obtained depending on the regio-selectivity of the reaction. Herein, we report our results on this novel ketenimine/1-azadiene four-component reaction.

We started our study with the ketenimines obtained from oxalic acid monoethyl ester chloride. These can be prepared directly



Scheme 1. Formation of ketenimines by a Nef/Perkow sequence.

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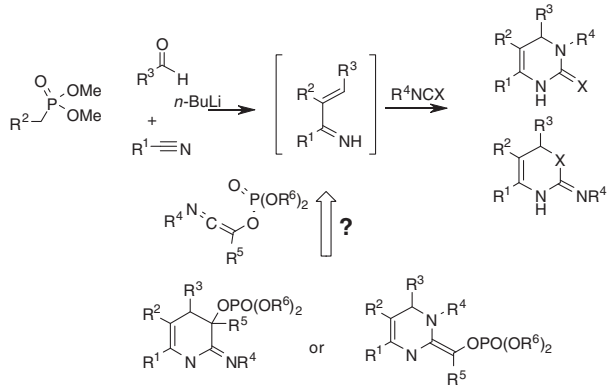
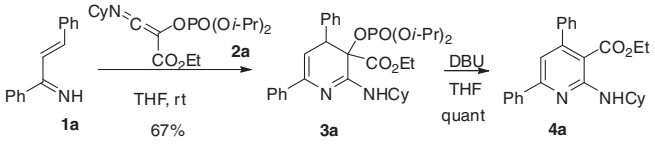
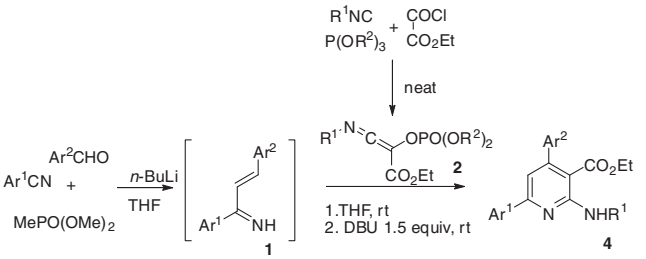


Scheme 2. 1-Azadiene formation and trapping.



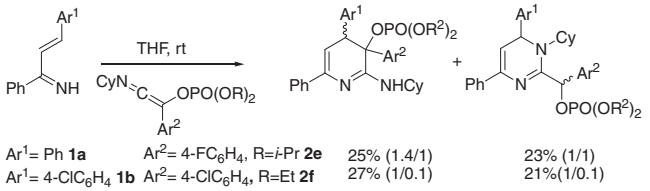
Scheme 3. Pyridine formation from **1a**.

Table 1
Pyridine synthesis from ketenimines **1** and azadienes **2**[9]



Entry	Azadiene	Ketenimine[a]	Product (yield %)
1	Ar^1, Ar^2 = Ph **1a**	**2a**	**4a** (68)
2	**1a**	**2b**	**4b** (58)
3	**1a**	**2c**	**4c** (37)
4	**1a**	**2d**	**4d** (39)
5	Ar^1 = Ph, Ar^2 = 4-ClC_6H_4 **1b**	**2a**	**4e** (48)
6	Ar^1 = 4-$MeOC_6H_4$, Ar^2 = Ph **1c**	**2a**	**4f** (47)

[a] Except for **2a** and **2c** which were quantitatively formed, ketenimines were purified on silica gel before use.



Scheme 4. Dihydropyridines and dihydropyrimidines from aryl ketenimines.

from the corresponding isocyanides and trialkyl phosphites and can be used without any further purification in the subsequent cycloadditions.

When ketenimine **2a** was added to preformed azadiene **1a** in THF and the mixture stirred overnight at room temperature, the dihydropyridine derivative **3a** was formed as a single diastereomer in 67% isolated yield (Scheme 3). Product **3a** could be converted quantitatively into pyridine **4a** under basic treatment with DBU.

Assuming that changes in the nature of the initial substrates might lead to dihydropyridines of moderate stability, we preferred to avoid their isolation and performed subsequent phosphate elimination by direct addition of DBU. Under these conditions, pyridine **4a** was obtained in 68% isolated yield from diethyl methylphosphonate. Various ketenimines and azadienes reacted similarly to give the corresponding pyridines in good to moderate yields (Table 1).

Besides carboethoxy substituted ketenimines **2a–d**, the Nef/Perkow sequence was also efficient for the formation of aryl substituted ketenimines. Consequently, the cycloadditions with these ketenimines and azadienes were studied under similar conditions. However, these reactions proceeded with less regio- and diastereo-selectivity than the MCR toward pyridines **4**. Indeed when ketenimine **2e** was added to azadiene **1a**, two sets of diastereomers were isolated in a moderate overall yield (Scheme 4). The two dihydropyridine diastereomers were obtained in 25% yield as a 1.4/1 mixture. Their formation may be explained by cycloaddition of **1a** to the carbon–carbon double bond of the ketenimine. On the other hand, formation of the dihydropyrimidine isomer (23% yield as a 1/1 mixture) most likely proceeds via the competing cycloaddition path involving the carbon–nitrogen double bond of **1a**. Ketenimine **2f** behaved similarly upon treatment with azadiene **1b**, albeit forming a mixture of regiomers with improved diastereo-selectivity (Scheme 4).

In conclusion, we have coupled two multicomponent processes to provide a new pyridine synthesis involving azadienes and ketenimines. Unifying different multicomponent reactions as a synthetic strategy for the construction of heterocyclic cores is an interesting approach to achieve complexity and diversity in synthesis.[10] More interestingly, we have shown that the regio-selectivity of the cycloaddition between the ketenimine and the azadiene could be controlled by the substitution pattern on the ketenimine with additions observed on the C=C and the C=N double bonds of the ketenimine.

Acknowledgments

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References and notes

1. See for example the May issue (5) of *Chem. Rev.* 2004, *104* (guest editor Katritzky, A.R), which is devoted entirely to heterocyclic syntheses.
2. See for example: *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley: Weinheim, 2005; Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89; Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471. and references cited therein.

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9. *Typical procedure for* **3a**: To a 0.2 M solution of diethyl methylphosphonate (1 mmol) in dry THF was added *n*-BuLi (1.2 equiv, 750 μL of a 1.6 M solution in petroleum ether). The mixture was stirred at −78 °C for 90 min. Benzonitrile (1.1 equiv) was then added and the mixture stirred at −78 °C for 45 min before being stirred at −40 °C for 1 h. Benzaldehyde (1.1 equiv) was added and the mixture stirred at −5 °C for 30 min before being stirred at room temperature for 90 min. A 1 M solution of keteneimine **2a** (1.2 equiv) in THF was then added and the mixture was stirred at room temperature overnight. The solvents were removed in vacuo to afford dihydropyridine **3a** as a brown oil after flash chromatography (0.39 g, 67%). ^{1}H NMR ($CDCl_3$; 400 MHz) δ 7.82 (d, J = 6.8 Hz, 2H), 7.40–7.32 (m, 4H), 7.26 (d, J = 6.8 Hz, 2H), 7.30–7.23 (m, 2H), 5.86 (d, J = 6.6 Hz, 1H), 5.83 (d, J = 5.6 Hz, 1H), 4.51 (octuplet, $J_{H-H} = J_{H-P}$ = 6.3 Hz, 2H), 4.41–4.32 (m, 1H), 4.27–4.15 (m, 2H), 4.17–4.06 (m, 1H), 2.22–2.12 (m, 1H), 2.09–1.99 (m, 1H), 1.83–1.59 (m, 4H), 1.53–1.15 (m, 4H), 1.24 (d, J = 6.3 Hz, 3H), 1.20 (d, J = 6.3 Hz, 3H), 1.18 (t, J = 5.1 Hz, 3H), 1.15–1.10 (m, 6H). ^{13}C NMR ($CDCl_3$; 100.6 MHz) δ 168.3 (d, J_{C-P} = 1.5 Hz), 153.7 (d, J_{C-P} = 4.4 Hz), 144.8, 139.3, 137.5, 130.5, 128.5, 128.4, 127.9, 127.8, 125.9, 104.0, 82.4 (d, J_{C-P} = 8.1 Hz), 73.7 (d, J_{C-P} = 5.9 Hz), 73.5 (d, J_{C-P} = 5.9 Hz), 62.8, 50.0, 47.7 (d, J_{C-P} = 5.1 Hz), 32.6, 32.5, 26.3, 25.1, 24.0 (d, J_{C-P} = 5.1 Hz), 23.7 (d, J_{C-P} = 5.1 Hz), 14.2. IR (thin film) 2932, 1680, 1575, 1546, 1266, 1227, 1129, 999. MS (DI, CIP NH_3) m/z 400 (M–HOPO(Oi-Pr)$_2$). *Typical procedure for* **4a**: The procedure for **3a** was initially followed. Then DBU (1.5 equiv) was added before purification and the mixture was stirred at room temperature for 90 min. The solvents were removed in vacuo to obtain pyridine **4a** as a light yellow oil after flash column chromatography (0.27 g, 68%). ^{1}H NMR ($CDCl_3$; 400 MHz) δ 8.09 (d, J = 8.1, 2H), 7.51–7.37 (m, 7H), 7.35–7.30 (m, 2H), 6.96 (s, 1H), 4.34–4.22 (m, 1H), 3.93 (q, J = 7.1 Hz, 2H), 2.21–2.13 (m, 2H), 1.87–1.78 (m, 2H), 1.73–1.65 (m, 1H), 1.56–1.26 (m, 5H), 0.73 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$; 100.6 MHz) δ 169.4, 158.0, 157.8, 154.6, 143.0, 139.4, 129.8, 128.9, 128.3, 127.9, 127.7, 127.5, 110.7, 105.4, 60.7, 49.8, 33.5, 26.5, 25.4, 13.5. IR (thin film) 2929, 1683, 1653, 1576, 1545, 1265. MS (DI, CIP NH_3) m/z 400.
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