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Alternative tandem cyclisation pathways in the reaction between imines and enones

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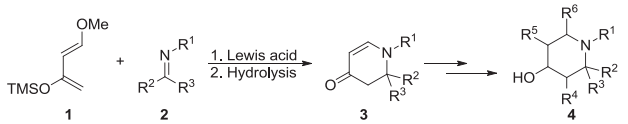
ABSTRACT

Dihydroisoquinoline reacts with Danishefsky's diene under Lewis acidic conditions or neat, to give low to moderate yields of the formal aza-Diels–Alder, [4+2]-cycloadduct. However, using methoxyvinyl methylketone with Lewis acid catalysis does not give the aza-Diels–Alder adduct, rather a formal [2+2+2]-cycloaddition occurs to provide access to a diacetyl dihydropyridine. Increased Lewis acid loading results in reduced dihydropyridine formation, and instead, a trimerisation reaction of the methoxyvinyl methyl ketone occurs, to give 1,3,5-triacetylbenzene from a different formal [2+2+2]-cycloaddition. The formal [4+2]-cycloaddition reaction of methoxyvinyl methylketone requires a cyclic imine in order to form the dihydropyridine because the reaction with acyclic imines produced a dihydropyridine from a formal [1+2+1+2]-cycloaddition. Evidence resulting from the isolation of reaction intermediates and in situ spectroscopic studies, shows that the reaction between 3,4-dihydroisoquinoline and methyl vinyl ketone, catalysed by oxy-philic Lewis acids, proceeds via a Mannich-Michael pathway and an imminium ion species. All reactions occur by one-pot cascade routes.

1. Introduction

Natural products containing the piperidine ring system[1] are well known to be biologically active[2] and many analogues have been developed for their potential medicinal properties.[3] The synthesis of these types of six-membered nitrogen heterocycles can be achieved via a Lewis acid-catalysed, formal aza-Diels–Alder reaction involving an imino dienophile and a conjugated diene[4] as outlined in Scheme 1 (e.g., using electron rich siloxy dienes such as Danishefsky's diene 1).[5]



Scheme 1. A general approach to poly-substituted piperidines.

The mechanism involved is potentially a concerted [4+2]-cycloaddition, however, in most cases it actually proceeds through a step-wise Mannich-Michael reaction.[6] Nevertheless, the formal Diels–Alder process is a powerful synthetic strategy for accessing piperidinones **3**, from, which more complex piperidines **4** can be accessed.[7]

As part of our ongoing development of novel approaches to piperidinones and their derivatives, typically employing Lewis acid catalysis[8] and associated mechanistic observations,[9] we have been examining the reactions of acyclic electron deficient imines with various dienes. In addition, we recognised the potential of this approach for the synthesis of polycyclic nitrogen-containing heterocycles of general type **6**, starting from cyclic imines. Heterocycles of this type occur naturally in representative structures with varied biological activity[10] and, hence, are worthy of further study in order to access formal aza-Diels–Alder adducts for elaboration to more substituted targets.

In this paper, we report the synthesis of *N*-heterocyclic compounds from imines and enones via different tandem cyclisation pathways. The different modes of reaction that we investigated include formal [2+2+2], [1+2+1+2] and [4+2] cascade cyclisations (see Scheme 2).

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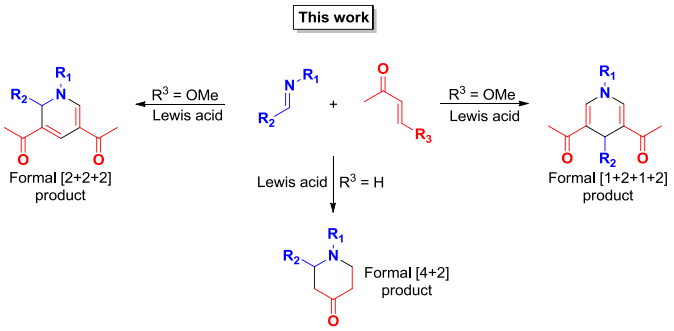
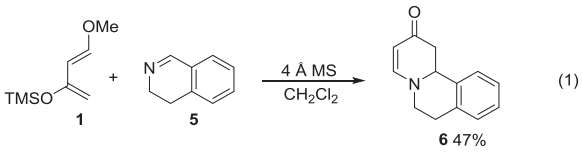


Scheme 2. The synthesis of *N*-heterocyclic compounds from imines and enones via different tandem cyclisation pathways.

2. Results and discussion

2.1. Synthesis of piperidenone and dihydropyridine analogues

Our starting point for the synthesis of piperidinones of type **3** was to examine the racemic formation of tricyclic piperidinone **6** as a prelude to developing a catalytic asymmetric route. Hence, we examined the reaction of Danishefsky's diene **1** under Lewis acid-catalysed conditions with readily accessible[11] imine **5** (Eq. 1).



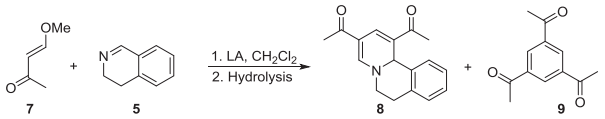
(1)

Danishefsky's diene reacted on its own with the imine, most likely initiated via nucleophilic attack of the diene on the imine, followed by cyclisation, i.e., through a Mannich-Michael mechanism.[6] After hydrolysis and purification, piperidinone **6** could be isolated in up to 47% yield. However, none of these reactions were completely clean according to TLC analysis, and therefore, an improved methodology to systems of type **3** was still required.

It was considered that direct reaction of 4-methoxy-3-buten-2-one **7** with imine **5** in the presence of a suitable catalyst might induce formation of an enolate equivalent in situ. This might be expected to cyclise to give the desired cycloadduct, hence, avoiding the use of Danishefsky's diene. This approach would be a stepwise addition, cyclisation, elimination, which nonetheless would accomplish the desired formal cycloaddition. Thus, exposure of 4-methoxy-3-buten-2-one **7** under a range of Lewis acid and secondary amine-catalysed reaction conditions was examined as in Eq. 2, resulting in complex mixtures of products. However, the use of ytterbium(III) triflate as Lewis acid catalyst did not provide piperidenone **6**. Instead, the diacetyl-dihydropyridine **8** was obtained in 20% yield; its structure was later proved by X-ray crystallography (see Supplementary data). The identification of product **8**, derived from a formal [2+2+2]-cycloaddition, through a cascade process, prompted us to examine this reaction in more detail.

2.2. Formal [2+2+2]-cycloaddition

The unexpected observation of the formation of the [2+2+2]-cycloaddition product **8** is almost unprecedented,[10] and therefore, further investigations into this reaction started by varying the catalyst and its loading. It was found that scandium(III) triflate was particularly effective for these reactions (see Eq. 2 and Table 1), however, a side-product **9** was observed, especially at higher catalyst loadings.



(2)

Table 1
Effect of catalyst loading on the reaction of **5** with **7** (Eq. 2)

Entry	Lewis acid (mol %)	Yield **8** (%)[a]	Yield **9** (%)[b]
1	0	0	—
2	5	<10[b]	—
3	10	61	—
4	20	48	<5
5	100	0	>55

[a] Isolated yield after silica gel chromatography.
[b] Conversion estimated from the crude ^{1}H NMR spectrum.

The high symmetry of the impurity meant that it was readily identified[12] as 1,3,5-triacetylbenzene **9** (the structure was also confirmed by X-ray crystallographic studies, see Supplementary data); a structure, which has been recently reported to readily assemble by heating 4-methoxy-3-buten-2-one **7** in water at 150 °C.[13] The results in Table 2 also show that the formation of trimer **9** was favoured over the formation of dihydropyridine **8** with increasing Lewis acid catalyst loading. Without the addition of Lewis acid, no reaction occurred (Table 1, Entry 1). With low Lewis acid catalyst loading (5%), low conversion to adduct **8** was observed (Table 1, entry 2). Optimal formation of dihydropyridine **8** occurred at 10 mol % catalyst loading, with no trimer **9** being produced (Table 1, entry 3). With 20 mol % catalyst loading, trimer **9** started to appear (Table 1, Entry 4), though to obtain complete conversion to the trimer alone, stoichiometric Lewis acid seemed to be required (Table 1, Entry 5).

As can be observed from Table 2, relatively low to moderate yields of the formal [2+2+2]-cycloadduct **8** were obtained, i.e., in the 20–40% range, though in a convenient manner and a pure form, through direct trituration of the crude reaction product. Despite the low yields obtained (Table 2), these studies provided some additional useful information about the catalytic process. The use of either $Sc(OTf)_3$, $Yb(OTf)_3$, or its hydrate as catalysts made little difference to the isolated yields (Table 2, entries 1, 3 and 5), with or

Table 2
Optimisation studies of the [2+2+2]-cycloaddition reaction to give **8**, as in Eq. 2

Entry	Enone equiv **7**	Catalyst (mol %)	Solvent	Time (days)	Additive	Yield **8** (%)[a]	Yield **9** (%)[b]
1	5	$Yb(OTf_3)$ (20)	CH_2Cl_2	2	—	40	<5
2	2	$Yb(OTf_3)$ (20)	$CDCl_3$	1	—	30	<5
3	2	$Sc(OTf)_3$ (10)	$CHCl_3$	2	—	41	0
4	2	$Sc(OTf)_3$ (10)	$CHCl_3$	2	4 Å MS	42	0
5	2	$Yb(OTf_3)$ hydrate (10)	$CHCl_3$	2	—	40	0
6	3	$Sc(OTf)_3$ (10)	$CHCl_3$	1–2	—	40	0
7	4	$Sc(OTf)_3$ (10)	$CHCl_3$	2	—	50	0
8	5	$Sc(OTf)_3$ (10)	$CHCl_3$	2	—	20	0
9	4	$Sc(OTf)_3$ (10)	EtOAc	3	—	20	0
10	4	$Sc(OTf)_3$ (10)	MeOH	3	—	15	0
11	4	$Sc(OTf)_3$ (10)	CH_3CN	3	—	15	0
12	4	$Sc(OTf)_3$ (10)	THF	3	—	30	0
13	4	$Sc(OTf)_3$ (10)	Et_2O	3	—	21	0
14	4	$Sc(OTf)_3$ (10)	Hexane	3	—	19	0
15	4	$Sc(OTf)_3$ (10)	CH_2Cl_2	3	—	21	0
16	4	$Sc(OTf)_3$ (10)	Toluene	3	—	20	0
17	4	$Sc(OTf)_3$ (10)	$CHCl_3$	3	H_2O	15	0
18	4	$Sc(OTf)_3$ (10)	$CHCl_3$	3	4 Å MS	25	0
19	4	$Sc(OTf)_3$ (10)	$CHCl_3$	3	—	20	0

[a] Isolated yield after work up by trituration.
[b] Conversion estimated from the crude ^{1}H NMR spectrum.

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