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A multicomponent formal [1 + 2 + 1 + 2]-cycloaddition for the synthesis of dihydropyridines†

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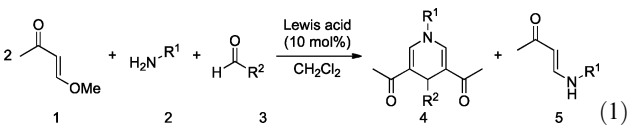
Reaction of methoxyvinylmethylketone with different amines and aldehydes under Lewis-acid catalysed conditions results in a novel, formal, step-wise [1 + 2 + 1 + 2]-cycloaddition to give dihydropyridine products.

The ability to perform atom-economic, multi-component reactions is increasingly important in order to quickly and efficiently construct target molecules.[1] Since the first reported multi-component Strecker reaction in the 19th century,[2] there have been many challenges, new developments and further examples reported. The fact that such reactions necessarily require many different components in the reaction mixture increases the possibility of unwanted competing side-reactions to occur. Hence, new multi-component reactions should ideally: (1) minimise side-product formation; (2) be general processes which work on a variety of substrates; and (3) be capable of including a range of functionality for further manipulation. There are many different examples of this requiring three components, for example, from the Mannich to the Biginelli reaction.[3] However, the use of four or more components is much less reported, and indeed, the list of known examples is notably small, including the Ugi, Passerini and Hantzsch pyridine protocols.[4] In this paper, a novel multi-component, formal [1 + 2 + 1 + 2]-cycloaddition process is reported which efficiently constructs dihydropyridine derivatives from amine, aldehyde and enone starting materials.

We have been interested in the synthesis of piperidine derivatives using a formal aza-Diels–Alder-type process for a number of years.[5] Many of these types of reactions rather than being a concerted cycloaddition, tend to occur *via* a stepwise Mannich-Michael pathway.[6] We were interested in developing new one-pot, rapid assemblies of piperdinones and related derivatives and were examining reactions of imines and diene precursors, *i.e.* enones. However, during these investigations it was found that under certain Lewis acid-catalysed conditions (where imine hydrolysis was possible), unexpected dihydropyridines were detected. A closer investigation involving the reaction of one equivalent of an amine **2** and aldehyde **3**, with two equivalents of 4-methoxy-3-buten-2-one **1** in the presence of a Lewis acid (see eqn (1)) formed the corresponding diacetyl dihydropyridine. The use of different amine and aldehyde combinations revealed the reaction to be reasonably general using $Sc(OTf)_3$, and after some limited optimisation (Lewis acid and loading, reactant ratios etc) a number of different examples could be accessed albeit over varying reaction times depending on the substrate combinations (see Table 1). Many of the products were also crystalline and hence, their structures were determined by single crystal X-ray diffraction (see Fig. 1 for example, and the Supplementary Information†).



(1)

At first glance, this reaction looks similar to the Hantzsch pyridine synthesis,[7] however, it almost certainly proceeds through a novel and different mechanism in order to give rise to the different dihydropyridines (*vide infra*). The use of an enone instead of an α-ketoester to form these types of dihydropyridines is almost unprecedented; to our knowledge only Inouye *et al.* in the late 50s briefly reported the most closely related example,[8] whereby 4-chloro-3-buten-2-one was employed instead of 4-methoxy-3-buten-2-one **1**.

In terms of the different aldehydes used (see Table 1), higher yields were generally obtained with aromatic aldehydes, whereas, for the amines, lower yields were obtained when either the amine was less nucleophilic (such as aniline, see Table 1, entries 6 and 7) or more bulky (such as *tert*-butylamine, Table 1, entries 13 and 14). In these cases, the reactions tended to stall at the initial Michael-addition step to form the vinylogous amides, *i.e.* resulting in the isolation of compounds **5a–d**. This could generally be overcome to some extent by heating the reaction to 60 °C, as in the case of Table 1, entry 14, however, this also resulted in the formation of the double vinylogous amide product **7** being formed as the major product. The best yield was obtained when

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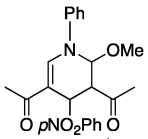
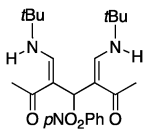
† Electronic supplementary information (ESI) available: full experimental details, characterisations, ^1H and ^{13}C NMR spectra for new compounds, and full crystallographic data (excluding structure factors) in CIF format for **4a** (two polymorphs), **4d**, **4e**, **4f**, **4g**, **4h**, **4i**, **4k** and **6**. CCDC 869480–869489. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc31495a

Table 1 [1+2+1+2]-Cycloadditions to form dihydropyridines of type **4** (see eqn (1)[a])

Entry	R^1	R^2	Time (days)	Cycloadduct isolated	Other products isolated
1	**2a** (R^1 = Bn)	**3a** (R^2 = *p*-NO_2Ph)	11	**4a** (86%)[b]	—
2	**2a**	**3b** (R^2 = Ph)	10	**4b** (59%)	—
3	**2a**	**3c** (R^2 = *p*-MeOPh)	13	**4c** (59%)	—
4	**2a**	**3d** (R^2 = Et)	19	**4d** (13%)[b]	**5a** (28%)
5	**2a**	**3e** (R^2 = $CH(OMe)_2$)	4	**4e** (42%)[b]	—
6	**2b** (R^1 = Ph)	**3a**	11	**4f** (31%)[b]	 **6** (27%)[b]
7	**2b**	**3f** (R^2 = ^{t}Bu)	14	—	**5b** (45%)
8	**2c** (R^1 = allyl)	**3a**	8	**4g** (62%)[b]	—
9	**2c**	**3b**	2	**4h** (58%)[b]	—
10	**2c**	**3c**	8	**4i** (34%)[b]	—
11	**2c**	**3e**	4	**4j** (20%)	—
12	**2d** (R^1 = Me)	**3d**	20	**4k** (28%)[b]	—
13	**2e** (R^1 = ^{t}Bu)	**3d**	17	—	**5c** (99%)
14	**2e**	**3a**	7	**4l** (30% at 60 °C in toluene)	 **7** (59%)
15	**2f** (R^1 = *p*-MeOPh)	**3b**	2	—[c]	**5d** (25%)

[a] All reactions were carried out using $Sc(OTf)_3$ as catalyst. [b] Denotes that single crystal X-ray structures obtained (see ESI†). [c] An inseparable mixture of cycloadduct and its MeOH adduct was obtained in *ca.* a 3:1 ratio in an estimated yield (by ^{1}H NMR) of 39%.

using benzylamine and *p*-nitrobenzaldehyde (Table 1, entry 1). Interestingly, when the role of the solvent was examined by running the reaction in different solvents and monitoring by TLC analysis after 48 h, and observing the complexity of product distribution, DCM appeared to provide the cleanest reactions compared with other solvents (DCM > THF > EtOAc > MeOH > toluene), as reported in Table 1.

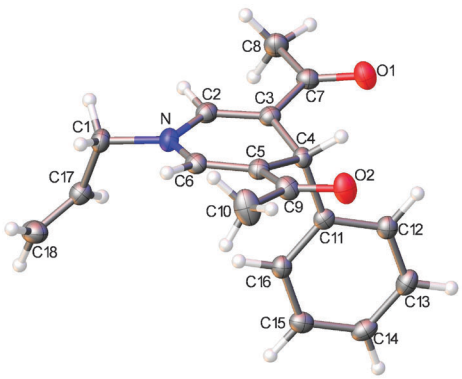


Fig. 1 X-ray-derived molecular structure of **4h** (Olex2 graphics).[10]

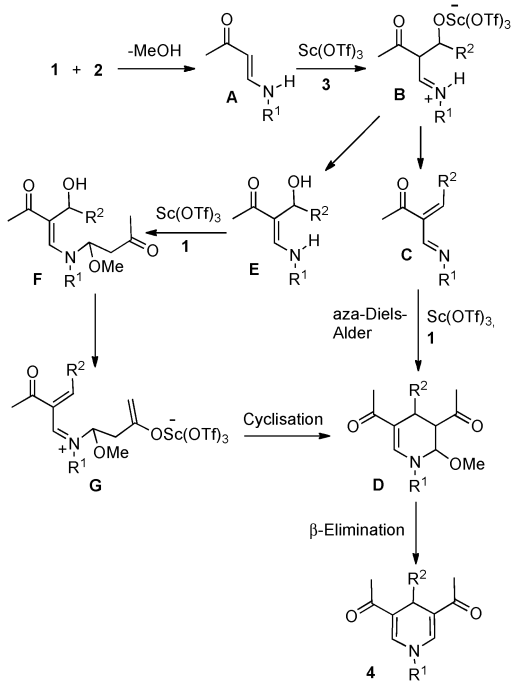
Table 2 Mechanistic studies for the [1+2+1+2]-cycloaddition reaction

Entry	Reaction
1	**1** + **2a** (2 : 1) $\xrightarrow[CDCl_3,\ 1\ d]{Sc(OTf)_3\ (10\ mol\%)}$ **5a** + **1** (50%[a] : 50%[a]) $\xrightarrow[2\ d]{\mathbf{3a}\ (1)}$ **4a** 60%[a]
2	**1** + **2a** (2 : 2) $\xrightarrow[CDCl_3,\ 1\ h]{Sc(OTf)_3\ (10\ mol\%)}$ **5a** 100%[a] $\xrightarrow[5\ d]{\mathbf{3a}\ (1)}$ **4a** 32%[a]
3	**1** + **2a** (2 : 2) $\xrightarrow[1\ h]{CDCl_3}$ **5a** 100%[a] $\xrightarrow[5\ d]{\mathbf{3a}\ (1),\ Sc(OTf)_3\ (10\ mol\%)}$ **4a** 33%[a]
4	**1** + **2a** + **3a** (1 : 1 : 1) $\xrightarrow[CDCl_3,\ 1\ d]{Sc(OTf)_3\ (10\ mol\%)}$? $\xrightarrow[5\ d]{\mathbf{1}\ (1)}$ **4a** 97%[a]

[a] Conversions estimated with respect to the amount of MeOH produced in the reaction, by ^{1}H NMR integration.

It is possible to be reasonably certain that the initial intermediate formed in these formal [1+2+1+2]-cycloaddition reactions is the vinylogous amide species, *i.e.* **5** (eqn (1)), for several reasons and from NMR studies reported in Table 2, since: (1) this intermediate has been isolated several times in these reactions, *i.e.* see Table 1, entries 4, 7, 13 and 15; (2) reaction of enone **1** (2 equiv.) with amine **2** (1 equiv.) in the absence of aldehyde gives the vinylogous amide and unreacted enone **1** (Table 2, entry 1) and subsequent addition of aldehyde gives rapid conversion to the cycloadduct (*ca.* 60%); (3) if the enone (2 equiv.) was reacted with the amine (2 equiv.), only the intermediate vinylogous amide was formed and addition of the aldehyde (1 equiv.) results in a less efficient formation of the dihydropyridine (Table 2, entry 2); (4) the vinylogous amide was formed even in the absence of a Lewis acid, as in Table 2, entry 3, and subsequent addition of aldehyde and Lewis acid provided the cycloadduct, though similarly less efficiently to entry 2 (Table 2); (5) the dihydropyridine ring was formed most efficiently and cleanly by reaction of enone (1 equiv.), amine (1 equiv.) and aldehyde (1 equiv.), followed by the addition of another equivalent of enone (See Table 2, entry 4).

These results strongly suggest that the order of events is as outlined in Scheme 1, rather than the related process examined by Inouye which is claimed to proceed through 2 equivalents of a vinylogous amide reacting with 1 equivalent of aldehyde.[9] We propose that intermediate **A** (*i.e.* 5) forms quickly and reacts with an aldehyde to give the key species **B** assisted by the Lewis acid. From this intermediate, it is likely that two possible pathways may then operate. Either a Diels–Alder cycloaddition pathway can occur *via* scandium-assisted oxide elimination to derive electron deficient aza-diene **C**,



Scheme 1 Proposed mechanism for the formal [1 + 2 + 1 + 2]-cycloaddition.

which could undergo inverse electron demand Diels–Alder cycloaddition with further enone to drive **D**, which can then eliminate; or, the enamine intermediate **B** can protonate (to give **E**) and react with the enone in a Lewis-acid assisted Michael addition process to derive **F**. This species then requires a cyclisation, presumably *via* an enolate equivalent cyclising onto an unsaturated iminium ion such as **G** to derive the same intermediate **D**, from which methanol elimination can occur.

Further evidence for the process outlined in Scheme 1 comes from the isolation of compound **6** in 27% from the reaction involving aniline and *p*-nitrobenzaldehyde (See Table 1, entry 6), which is a clear example of the importance of species **D** in Scheme 1. Single crystal X-ray analysis clearly reveals that this compound is as shown in Fig. 2 and must correspond to the last intermediate before β-elimination occurs to give the dihydropyridine, as outlined in Scheme 1.

To conclude, we have shown a general multi-component synthesis for the formation of dihydropyridines through a [1 + 2 + 1 + 2]-cycloaddition pathway. After optimisation, the dihydropyridine ring can be formed with high conversion within a week.

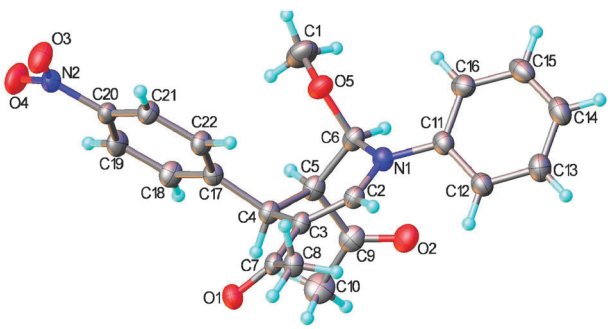


Fig. 2 X-ray molecular structure **6** (Olex2 graphics).[10]

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