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Synthesis of highly functionalized 1,6-dihydropyridines via Zn(OTf)₂-catalyzed three-component cascade reaction of aldimines and two alkynes (IA²-coupling)

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A zinc(II) triflate catalyzed three component synthesis of 1,6-dihydropyridines, involving aldimines, alkynes and electron deficient dimethyl acetylenedicarboxylate (DMAD), in good to excellent yields has been described. Besides a range of different N-substituents, a variety of both aromatic and aliphatic alkynes could be used. The application of electron deficient propiolates instead of DMAD, gave rise to regiospecific incorporation of the ester functionality on the 1,6-dihydropyridine ring. The reaction proceeds via a cascade involving nucleophilic addition of the metal acetylide to the imine, followed by addition of the intermediately formed propargylic amine to the electron deficient alkyne and subsequent 6-*endo dig* cyclization.

Introduction

Among the aza-heterocyclic compounds, pyridines are extensively used motifs in synthetic organic chemistry and in pharmaceuticals.¹ Dihydropyridines (DHPs) are organic scaffolds based on pyridine and from a synthetic point of view DHPs serve as a platform for the synthesis of highly functionalized piperidines and pyridines; the ever-ubiquitous framework of natural products and medicinal drugs.² Among the various isomers of DHPs, 1,2- and 1,4-dihydro isomers constitute the most prevailing groups. 1,2- or 1,6-Dihydropyridines can be converted to other aza-heterocyclic compounds³ such as indolizines, quinolizidines and isoquinuclidines.³ Traditionally dihydropyridines have been accessed by either condensation reactions of amines and carbonyl compounds, by partial reduction or nucleophilic addition to pyridines and pyridinium salts, or by pericyclic reactions (cycloaddition and Diels-Alder reactions). Condensation reactions of carbonyl compounds and amines lead to symmetrical 1,4-dihydropyridines, the main method to access this class being the Hantzsch synthesis.⁴ The high interest for this class can be explained by their activity as calcium channel blockers.⁵ The partial reduction of pyridines and pyridinium salts is a non-selective

method and always suffers from regioisomeric mixtures. Alternatively, 1,6-DHPs are synthesized by the nucleophilic addition onto pyridinium salts,⁶ which also results in the formation of inseparable regio-isomeric mixtures of adducts at the C2, C4, or C6 positions.

Although 1,4-dihydropyridines have attracted much more attention due to their wide biological and pharmaceutical applications,^{7,5} the biological applications of 1,2-/1,6- DHPs remained largely unexplored. Some 1,2-dihydropyridine derivatives have been disclosed as potential anticancer⁸ and anti ulcer agents.⁹ Despite their potential biological and synthetic utility, methodologies to 1,2- or 1,6-dihydropyridines remain underdeveloped¹⁰ as compared to their 1,4-regioisomers, primarily because of the more challenging regioselectivity.

Yoshikai *et al.* developed a Ni-catalyzed [2+2+2]-cycloaddition between imines bearing a *N*-pyridyl group and alkynes to afford 1,2-dihydropyridines. Further variation of the alkyne moiety is not possible because of regioselectivity problems (Scheme 1, equation a).¹¹ Jin *et al.* reported the reaction of preformed propargylamines with dimethyl acetylenedicarboxylate (DMAD) or methyl propiolate to deliver polysubstituted pyrroles. When methyl 2-butyrate in combination with terminal propargylic amines were reacted, a 50/50 mixture of 1,2,3,4-tetrasubstituted and 1,2,3,5-tetrasubstituted pyrroles were obtained (Scheme 1, equation b).¹² Related to this work is the base promoted synthesis of pyrroles from 3-aza-1,5-enynes, which are the formal additon products of propargylamines with methyl propiolates.¹³ On the other hand simple heating of these *N*-tosyl-3-aza-1,5-enynes in methanol gave the 1,2-dihydropyridines.¹⁴ An alternative method to access 1,6-DHPs with flexible and regio-controlled

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Previous work

Scheme 1 Previous syntheses of 1,2-dihydropyridines from imines and alkynes.

installation of substituents on the N1, C2, C3, C4, and C6 positions, is the Cu(I)-catalyzed 6-*endo* cyclization of propargylic enamino carbonyls as reported by the Oguri group (Scheme 1, equation c).¹⁵ The reaction between α,β -unsaturated imines and alkynes via the 6π -electrocyclization of an intermediate aza-triene in the presence of a low valent cobalt complex $[\text{Co}(\text{PMe}_3)_4]$ ¹⁶ or a $[\text{RhCl}(\text{coe})_2]_2$ catalyst¹⁷ lead to regioselective 1,2-DHPs formation. This method proved straightforward compared to other approaches, where screening of ligands, reducing agents, and sometimes additives is required (Scheme 1, equation d).

Despite all these efforts, the preparation of selective non-symmetrically substituted dihydropyridines is a major challenge in synthesis. For these reasons, the development of alternative methods for the selective synthesis of 1,2- or 1,6-dihydropyridines from readily available starting materials continues to be of intense interest.

Herein we describe a novel, general and potentially more efficient synthetic route toward 1,6-dihydropyridines starting from imines and two different alkynes (IA²-coupling) through a Zn(II)-catalyzed cyclization.

Results and discussion

Several tandem reactions based on a A3 coupling as the key transformation have been devised, in particular for the synthesis of more complex and structurally diverse

heterocyclic products in one pot.¹⁸ As Multi Component Reactions (MCR) are attractive for the synthesis of complex molecules by avoiding several reaction steps,¹⁹ initial investigations to access the dihydropyridine started with a one pot reaction. Dimethylpropanal (**1a**), *n*- propylamine (**2a**), phenylacetylene (**4a**) and DMAD (**5a**) (A⁴-coupling) were reacted in the presence of 20 mol % ZnCl_2 and magnesium sulfate as a drying agent in dichloromethane. After work up not even a trace of the envisioned product **6a**, or any

Scheme 2 Attempted one pot synthesis of dihydropyridines **6a**.

other compound was obtained (Scheme 2). Other catalysts such as $\text{Zn}(\text{OTf})_2$ and $\text{Cu}(\text{OTf})_2$ in the presence of 4 Å molecular sieves as dehydrating agents and toluene as solvent, besides some traces of the propargylic amines **7** also did not show any product (Scheme 2).

Table 1 Optimization of IA²-coupling for synthesis of dihydropyridine **6a**

Entry	Catalyst/mol %	T/t (°C/h)	Solvent (1 mL)	Yield 6a (%) ^a
1	$\text{ZnCl}_2/20$	100/24	PhMe	65 ^b
2	$\text{ZnCl}_2/20$	50/24	CH_2Cl_2	NR ^c
3	$\text{ZnCl}_2/20$	100/24	DMF	76
4	$\text{ZnCl}_2/20$	65/24	THF	45
5	$\text{ZnCl}_2/20$	90/16	2-MeTHF	54
6	$\text{ZnCl}_2/20$	100/16	PhMe/DMF (1/1)	78
7	$\text{ZnCl}_2/20$	100/24	PhMe/DMF (7/3)	88
8	$\text{ZnBr}_2/10$	100/24	PhMe/DMF (7/3)	80
9	$\text{ZnI}_2/10$	100/24	PhMe/DMF (7/3)	66
10	$\text{Zn}(\text{OAc})_2/10$	100/24	PhMe/DMF (7/3)	Complex
11	$\text{Zn}(\text{OTf})_2/10$	100/24	PhMe/DMF (7/3)	95
12	$\text{Cu}(\text{OTf})_2/10$	100/24	PhMe/DMF (7/3)	55 ^{d,e}
13	$\text{CuBr}_2/10$	100/24	PhMe/DMF (7/3)	47 ^e
14	$\text{Zn}(\text{OTf})_2/5$	100/24	PhMe/DMF (7/3)	87 ^f
15	$\text{Zn}(\text{OTf})_2/10$	100/6	PhMe/DMF (7/3)	59 ^g
16	$\text{Zn}(\text{OTf})_2/10$	100/18	PhMe/DMF (7/3)	95
17	-	100/24	PhMe/DMF (7/3)	NR ^c
18	$\text{Zn}(\text{OTf})_2/10$	100/24	PhMe	61

^a Isolated product. ^b Traces of **7** were present. ^c NR = no reaction. ^d 20 % of **7**. ^e Reaction was performed under argon. ^f 5 % of **8** was present (¹H NMR). ^g 30 % of **8** was present.

When the reaction was performed with preformed aldimine, namely 2,2-dimethyl-*N*-propylpropan-1-imine (**3a**), with phenylacetylene (**4a**) and DMAD (**5a**) in toluene, we were gratified to observe a 65% yield of the expected dimethyl 6-(*tert*-butyl)-4-phenyl-1-propyl-1,6-dihydropyridine-2,3-dicarboxylate (**6a**), along with some traces of propargylamine **7** (Table 1, entry 1). In order to perform this reaction under milder conditions, CH₂Cl₂ was used as a solvent and the reaction mixture was heated at 50 °C, but no reaction occurred at all (Table 1, entry 2). By using a polar and coordinating solvent such as DMF, the yield of the dihydropyridine **6a** could be improved to 76%, but the ¹H-NMR spectrum was not clear due to unidentified peaks (Table 1, entry 3). Other coordinating solvents like THF and 2-MeTHF proved less efficient and unreacted imine and alkyne were recovered (Table 1, entries 4-5).

Keeping in mind the improved yield in DMF and cleanliness of the reaction in toluene a combination of both solvents was evaluated. As an initial test, a 1/1 ratio of DMF/toluene was used, giving a 78% yield of the desired 1,6-dihydropyridine **6a**, without any starting material left in the reaction mixture (Table 1, entry 6). Encouraged by this result, different ratios of toluene and DMF were tested to improve the yield. The most promising ratio was toluene/DMF 7/3, which provided 88% yield of **6a** (Table 1, entry 7).

With a good solvent combination established, different catalysts were tested. Other Zn(II)-salts such as ZnBr₂, ZnI₂ and Zn(OAc)₂ proved less or not efficient. Using ZnBr₂ and ZnI₂ (10 mol %) in 7/3 ratio of toluene and DMF, decreased yield was observed, while Zn(OAc)₂ gave a complex reaction mixture (Table 1, entries 8-10). A remarkable improvement in yield was observed when Zn(OTf)₂ was used as catalyst. Using Zn(OTf)₂ 10 mol % in toluene and DMF at 100 °C for 24 h gave 95% yield of **6a** (Table 1, entry 11). Copper salts such as Cu(OTf)₂ and CuBr₂ delivered the expected product **6a** in a reduced yield of 55 and 47% respectively (Table 1, entries 12-13). Therefore, Zn(OTf)₂ was selected as the optimal catalyst for this reaction. By further reducing the amount of catalyst from 10 mol % to 5 mol % and by reducing the reaction time, a lower yield of **6a** was observed (Table 1, entries 14-15). Besides **6a**, a reactive intermediate, dimethyl 2-((4,4-dimethyl-1-phenylpent-1-yn-3-yl)(propyl)amino)maleate (**8**) was observed in the reaction mixture. The enamine type intermediate **8** was separated from the main product **6a** and was fully characterized by NMR spectroscopy and HRMS. The formation of this intermediate gave an indication for the mechanism of the formation of 1,6-dihydropyridines **6** (Scheme 4). Reducing the reaction time to 18 h almost did not affect the yield of the 1,6-dihydropyridine (**6a**) (Table 1, entry 16). When no catalyst was used, no reaction at all was observed (Table 1, entry 17). Thus, optimum conditions turned out to be heating together 1 equiv of aldimine (**3a**), phenylacetylene (**4a**) and DMAD (**5a**), using 10 mol % zinc(II) triflate in toluene/DMF (7/3) at 100 °C for 18 h. Under these conditions no presence of the intermediate compound **8** could be detected and therefore they were used for the substrate scope investigation.

At first instance, different aldimines and ketimines were tested to see the scope of reaction for substituents at 6-position of 1,6-dihydropyridine (at saturated carbon). It was observed that imine **3b** derived from *isobutyraldehyde* reacted well with phenylacetylene **4a** to give 1,6-dihydropyridines **6b** in excellent yield (Table 2). Imines derived from *n*-butyraldehyde or benzaldehyde did not afford the expected product and complex reaction mixtures were obtained which were not further analyzed.

Table 2 Synthesis of 1,6-dihydropyridines with various nitrogen substituents

^a Yields after column chromatography, reactions were carried out on 0.5 mmol scale of aldimine **3**. ^b NR = no reaction.

Imines derived from pivaldehyde and allylamine (**3c**), *i*-amylamine (**3d**) and benzylamine (**3e**) all reacted well with DMAD and phenylacetylene to deliver the expected 1,6-dihydropyridines in good yields (Table 2, **6c-6e**). Imines bearing secondary *N*-substituents like cyclohexyl (**3f**) and isopropyl (**3g**) also furnished the corresponding dihydropyridines **6f** and **6g** in good yields (Table 2, **6g-6h**). Only in case of *N*-*tert*-butyl aldimine (**3h**), no dihydropyridine was obtained. To determine whether the coupling of the alkyne **4a** to the imine or the *N*-alkenylation of the intermediate propargyl amine **9** is the limiting step, *N*-(*tert*-butyl)-4,4-dimethyl-1-phenylpent-1-yn-3-amine (**9**) was prepared independently²⁰ and reacted with DMAD. No reaction was observed, which may be explained by the additional sterical hindrance of the *N*-*t*-butyl group in **9** (Scheme 3).

The structure of the 1,6-dihydropyridine compound **6d** was further confirmed by using single-crystal X-ray structure analysis (Fig. 1). The crystal structure is racemic, but contains two symmetry independent molecules (*Z'*=2). It can be obtained from the CCDC under CSD deposition number 1814906.

Next, the substrate scope with respect to the alkyne component was explored; both aromatic and aliphatic alkynes could be used under the optimum reaction conditions. It was found that the method is equally general for electron donating groups on phenylacetylene like 3-methyl (**4b**), 4-ethyl (**4c**) and for mild electron withdrawing groups e.g. 4-chloro- (**4d**) and 4-bromo- (**4e**) phenylacetylene (Table 3, **6i-6l**). 2-Naphthylacetylene (**4f**) also delivered the 1,6-dihydropyridine **6m** together with substantial amounts of the corresponding precursor enamine, which unfortunately could not be removed by any means of chromatography (Table 3).

Scheme 3 Synthesis of *N*-tert-butyl-1,6-dihydropyridine.

Fig. 1 Single-crystal X-ray structure of **6d**. The asymmetric unit is shown ($Z'=2$). Displacement ellipsoids are at the 50% level, H atoms have been omitted for clarity.

Table 3 Synthesis of 1,6-dihydropyridines with various alkyne components

^a Yields after column chromatography, reactions were carried out at 0.5 mmol scale of aldimine **3**. The reaction time is given in brackets. ^b ND=yield not determined.

Scheme 4 Synthesis of methyl 1,6-dihydropyridine-3-carboxylate.

Even electron rich acetylenes like 2-methoxy- (**4g**) and 4-methoxyphenylacetylene (**4h**) as well as 6-methoxynaphthylacetylene (**4i**) did react very well under the conditions developed to furnish the expected dihydropyridines in good yields (Scheme 3, **6n-6p**).

Phenylacetylenes substituted with strong electron withdrawing group like 4-CF₃ (**4j**) gave a slightly lower yield of 44% (Table 3, **6q**). Besides aromatic, also aliphatic alkynes reacted to deliver the expected 1,6-dihydropyridines. For example, 1-pentyne (**4k**), cyclohexenylacetylene (**4l**), and alkynes containing an ester functionality (**4m**) gave the desired dihydropyridines in good to moderate yields (Table 3, **6r-6t**). Next, the regioselectivity of the one pot reaction was evaluated by reaction of aldimine **3a** with methyl propiolate (**5b**) and phenylacetylene (**4a**). The reaction of pivaldimine

(**3a**), phenylacetylene (**4a**) and methyl propiolate (**5b**), using 10 mol % zinc(II) triflate in toluene/DMF (7/3) at 100 °C for 18 h gave rise to methyl 6-(*tert*-butyl)-4-phenyl-1-propyl-1,6-dihydropyridine-3-carboxylate (**10a**) in 45% yield, besides methyl propiolate (**5b**) and propargylamine **7**. The regioisomeric dihydropyridine **10a'** was not observed. To force the reaction to completion a small adjustment in the reaction conditions was made with respect to solvent, temperature and the amount of methyl propiolate (see Table S1 in SI). The application of an excess of 1.5 equivalents of methyl propiolate (**5b**) and heating at 110 °C for 24 h in pure DMF instead of a toluene/DMF mixture gave only one product **10a** in 89% yield (Scheme 4).

The substitution pattern of the dihydropyridine monocarboxylate **10a** was confirmed by X-ray crystallography and clearly showed the methoxycarbonyl group at the 3-position (see Figure 2). The crystal structure is racemic, but the unit cell contains two symmetry independent molecules ($Z'=2$) that are nearly equivalent by inversion, except for the orientation of the ethyl group. It can be obtained from the CCDC under CSD deposition number 1814907.

By utilizing these conditions the coupling of *N*-benzylaldimine (**3e**) with phenylacetylene (**4a**) and methyl propiolate (**5b**) also delivered the corresponding 1,6-dihydropyridine **11** in 65% yield. Extension of this method to internal electron poor alkynes, like ethyl 2-butyrate (**5c**), required prolonged heating for 48 hours to complete the reaction and to deliver the expected 1,6-dihydropyridine **12** in 63% yield after chromatography. The reaction with ethyl phenylpropiolate (**5d**) only afforded traces of the dihydropyridine **13**.

Fig. 2 Single-crystal X-ray structure of **10a**. The asymmetric unit is shown ($Z'=2$). Displacement ellipsoids are at the 50% level, H atoms have been omitted for clarity.

A plausible mechanism was proposed for this transformation (Scheme 5). The first step is the formation of propargylamine **7** by zinc catalyzed alkynylation of imine **3** by alkyne **4**.²⁰ Propargylamines have often been used for the synthesis of various heterocycles.²¹ Nucleophilic addition of this amine to the electron-deficient alkyne leads to enamine **8**. The acetylenic moiety of **8** then coordinates with the Zn(II) favoring the 6-*endo dig* cyclization. Prototropy followed by protodemetalation furnishes the final dihydropyridine **6**. The alternative base-induced 5-*exo dig* cyclization as reported in the literature for terminal propargylic amines,^{12,13} and *N*-propargylic β -enaminones²² would give rise to substituted

Table 4 Synthesis of 1,6-dihydropyridines with terminal and internal alkynoates^a

^a Yields after column chromatography, reactions were carried out at 0.5 mmol scale of aldimine **3**. The reaction time is given between brackets.

pyrroles **16**, and was never observed in any of the presented reactions. Clearly, in order to promote the formation of dihydropyridines the presence of a transition metal like Cu(I)^{15,22,23,24}, Au(I)²⁴ or Zn(II) as shown in the present work, is required. In a control experiment propargylamine **7** was synthesized independently²⁰ and reacted with DMAD in the presence of Zn(OTf)₂ in DMF/toluene at 100 °C for 18 h. The dihydropyridine **6a** was isolated in 95% yield. Enamine **8**, obtained earlier in a pure form from the optimization reactions, remained intact upon heating in DMF/toluene, while heating enamine **8** in the presence of 0.1 equivalents of Zn(OTf)₂ in DMF/toluene at 100 °C for 18 h gave rise to dihydropyridine **6** in a nearly quantitative yield. This reaction proves the dual role of zinc in this process, i.e. first catalysing the alkynylation reaction of the imine and secondly catalysing the ring closure to 1,6-dihydropyridines.

Scheme 5 Plausible mechanism for the synthesis of 1,6-dihydropyridines **6**.

Conclusions

In summary, a one pot transformation of aldimines, alkynes and electron deficient alkynes (IA² coupling) to regiospecifically substituted 1,6-dihydropyridines has been developed. This transformation takes place via an intermediately generated propargylamine, which forms an

enamine upon addition to the electron deficient alkyne. After 6-*endo dig* cyclization and proton transfer the final product is formed. Both the propargylamine formation as the cyclization are catalyzed by Zn(II). The method is general for a variety of N-substituents on the imine and several alkynes could be applied. Both terminal and internal electron deficient alkynes can be used, although more sterically hindered groups such as phenyl showed poor reactivity in case an internal alkyne was used.

Conflicts of interest

There are no conflicts to declare.

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