Pyridines via solid-supported [2 + 2 + 2] cyclotrimerization[†]

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The formation of pyridines *via* a crossed [2 + 2 + 2] cycloaddition has been achieved on a solid-support for the first time.

We recently initiated a program in developing solid-supported multicomponent reactions (MCRs)¹⁻⁶ for the rapid construction of small molecule libraries. This approach combines the advantages of solid-supported chemistry (easy automatization, parallelization, and purification)⁷⁻⁹ with the high convergence of MCRs. A classical MCR, the [2 + 2 + 2] cyclotrimerization towards highly substituted pyridine rings has surprisingly not received much attention in combinatorial chemistry.¹⁰⁻¹³ The commercial availability of a wide range of alkynes and nitriles makes this reaction an ideal candidate for the rapid assembly of diverse heterocyclic libraries.^{9,14} Pyridine rings are found in many biologically relevant structures including compounds with antiviral (HIV),15 antimicrobial,^{16,17} anticancer,¹⁸ and protein kinase inhibition activity.^{16,17} Catalyst systems applied in cyclotrimerizations towards pyridine synthesis are mainly based on cobalt, and recent developments have led to mild reaction conditions applicable to organic synthesis.^{19,20,21-26} However, major problems are still associated with this reaction, including chemo- and regioselectivity issues.^{13,27} The catalytic solution-phase cyclotrimerization of two alkynes and a nitrile results in the formation of mixtures of products including crossed pyridines (from the incorporation of two different alkynes) and homo pyridines (from the incorporation of two identical alkynes), as well as potential benzene byproducts. We resolved these problems by immobilizing one alkyne reaction partner on a polystyrene resin, thereby accomplishing the first catalytic crossed cyclotrimerization of this type. Specifically, propargyl alcohol was immobilized on a polystyrene resin (100-200 mesh)²⁸ using an acid labile trityl linker^{29,30} under standard conditions (pyridine, THF, rt, 12 h). Resin 1 was obtained with a loading of 0.8 mmol g^{-1} as determined by GC-MS analysis of a sample cleaved with 1% TFA in CH₂Cl₂.

Scheme 1 illustrates the generalized reaction of 1 with an alkyne 2 and a nitrile 3 yielding the immobilized pyridine 4. Only one regioisomer is displayed; however, regioselectivities observed in solution-phase reactions are typically low.^{11–13} The resin 1 was swelled in degassed toluene in the presence of the alkyne 2, the nitrile 3 (1 : 10 ratio to favor pyridine formation), and

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additive. The reaction mixture was heated to 80 °C and CpCo(CO)₂ (20 mol%) was added every 12 h for 48 h. Due to the pseudo-high dilution conditions on the resin surface, no pyridines resulting from the double incorporation of 1 were observed. Moreover, pyridines that result from the cyclotrimerization of two molecules of 2 and one molecule of 3 were removed in the workup step since they are not immobilized on the resin. The formation of benzenes through the reaction of 1 with two alkynes 2 was suppressed by using the catalyst $CpCo(CO)_2$ which favors pyridine formation in conjunction with an excess of nitrile 3^{13} Therefore a highly chemoselective crossed [2 + 2 + 2] cycloaddition towards 4 was achieved. The pyridine was then cleaved under mild conditions using 1% TFA in DCM yielding clean TFA-salts of the products 5. These salts were converted into the free bases by passing them through an ion exchange resin (Dowex 50WX8-100). The pyridines 5 were then analyzed by ¹H NMR, LC-MS, and GC-MS. They are observed in 43-85% yield (typical solutionphase yields are about 65%13) and excellent purity of generally >90%. By using a set of six different alkynes (6-11) and three different niriles (12-14) an array of 18 pyridines (15-32) was rapidly assembled. The reaction tolerates a variety of substituents, including alkyl groups (Me, Et, and Bu), aryl groups (Ph), hydroxy groups, alkoxy groups (CH₂OMe), and carbamates (BocNH). Free amines were not compatible with the reaction conditions; however, the Boc protecting group was conveniently removed from the corresponding carbamate in the cleavage step. Even alkynes which are less reactive due to sterical demand (9) or an internal triple bond (11) underwent cyclotrimerization. Crossed cyclotrimerizations lead to the formation of complex mixtures of

tetramethylammonium oxide (TMAO)³¹ as a catalyst activating





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Fig. 1 Alkynes (6–11) and nitriles (12–14) employed in solid-supported [2 + 2 + 2] cyclotrimerizations with 1 yielding pyridines 15–32. Yields and ratios of regioisomers are shown in parentheses. The regioisomeric ratios were determined by GC-MS (compounds 15–20, 23–29, and 32) and ¹H NMR (21–22 and 30–31) analysis. The structure of only one (out of several possible) 2,4,6-regioisomer is shown. 2,4,6-Regioisomers generally represent the major substitution pattern as determined for 21–23 by ¹H NMR. Compound purities are generally >90% as determined by GC-MS and ¹H NMR.

regioisomers, which can be explained with a generally accepted reaction mechanism (see Supplementary Data[†]).¹³ In these cases an assignment of regioisomers was not possible by spectroscopic means and a chromatographic separation was not feasible. However, the alkyne reaction partners 8 and 11 greatly simplify the formation of possible regioisomers and allow for an assignment of the major pyridine (the structure shown in Fig. 1). In the case of 8, a regioselectively less challenging homocyclotrimerization was performed leading to the predominant formation (67-90%) of the 2,4,6-substituted homo-pyridines 21-23. This is in agreement with literature observations in the solution phase.¹³ The reaction proceeds through a 2,4-disubstituted cobaltacyclopentadiene as the major reactive species followed by regioselective insertion of the nitrile under carbon-carbon bond formation with the less sterically hindered C-atom attached to the metal (see Supplementary Data[†]). The 2,3,6-trisubstituted pyridine (not shown) is the minor regioisomer (10-33%).

In the case of a crossed [2 + 2 + 2] cyclotrimerization with the symmetrical alkyne **11**, only two regioisomeric pyridines were obtained with the shown 2,3,4,6-pyridines **30–32** (Fig. 1) being the major isomers and the 2,3,5,6-pyridines (not shown) being the minor isomers. This regioselectivity was established *via* extensive NMR experiments and can be explained by the mechanism depicted in Scheme 2.





Using a symmetric and a terminal alkyne, two regioisomeric cobaltacyclopentadienes 33 and 34 can be potentially formed. However, the 2,3,4-cyclopentadiene 34 is the minor isomer due to steric interactions between the A and the B substituent. The major 2,3,5-isomer 33 reacts with the nitrile towards the regioisomeric 2,3,4,6- and 2,3,5,6-pyridines, 35 and 36 respectively. The regioisomers 37 and 38 were not observed in the cyclotrimerizations described in Fig. 1. The ratio of 35/36 was about 2 : 1 due to similar sterical demand of the two substituents. The slightly higher amount of 35 can potentially be attributed to the sterical demand of the trityloxy group. We are currently designing novel linker strategies in which the substituent A consists of sterical demanding groups thereby imposing a high regioselectivity on the reaction leading to the predominant formation of 35. Ideally, these linker groups will be cleaved in a traceless fashion.

In summary, we demonstrated the first crossed [2 + 2 + 2] cyclotrimerization reaction leading to the formation of highly substituted pyridines. The reaction was conducted on a solid-support facilitating its application in the multi-component synthesis of combinatorial libraries with good yields and excellent purities. We are currently expanding its scope by using additional reaction partners (*e.g.* isocyanates) and are synthesizing a variety of small molecule arrays. The obtained heterocyclic structures will be subsequently screened for biological activity.

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