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Efficient synthesis of 3-cyano-6-(2-hydroxyphenyl)pyridines by multi-component condensations on beads

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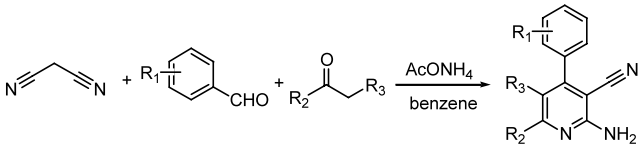
Abstract—An efficient procedure to perform pyridine ring closure reactions has been developed on beads. A certain number of hydroxyacetophenones were immobilized on Wang resin and condensed with a variety of aldehydes and malononitrile in the presence of ammonium acetate to give 3-cyano-6-(2-hydroxyphenyl)pyridines in a suitable manner for a good example of combinatorial approaches. Chemical yields were better than the corresponding solution-phase chemistry except only a few examples and the best use of inherent advantage of solid-phase chemistry was successfully demonstrated.

Heteroaromatic rings containing nitrogen atoms often play important roles as the scaffolds of bioactive substances.[1] Pyridine is one of the most popular *N*-heteroaromatics incorporated into the structure of many pharmaceuticals. Therefore, development of efficient procedures towards functionalized pyridines is a quite attractive target for solid-phase combinatorial chemistry. There are several papers presented about solid-phase synthesis of pyridines and they are categorized by the following three types: (i) Knoevenagel and Hantzsh condensation chemistry from β-keto esters,[2–4] (ii) '3+3' pyridine synthesis from α,β-unsaturated ketones,[5,6] (iii) Krohnke type cyclization with 1,5-diketone and ammonium acetate.[7] However, these methods have a limitation on the applicable building blocks and none of them were suitable to the analogue syntheses of 2-amino-3-cyano-4-(3-(5-oxo-2-tetrahydrofuran)carboxyanilido)-6-(2-hydroxyphenyl)pyridine that was recently identified as a primary hit of IKK-β inhibitors.[8] In solution-phase approaches, Kambe et al.[9] reported multi-component condensation reactions of malononitrile, aromatic aldehydes and alkyl ketones in the presence of ammonium acetate, as shown in Scheme 1. It is well known that multi-component condensations, such as Ugi reaction, are quite efficient tools to prepare a compound library in combinatorial fashion.[10,11] However, when this procedure was applied to our lead optimization, mess reaction mixtures were obtained in almost all of the cases and hardly purified by column chromatography, perhaps due to the poor solubility in usual organic solvents. In order to prevent this problem and prepare a series of 3-cyano-6-(2-hydroxyphenyl)-pyridines in a short period, we modified the procedure by solid-phase chemistry. This approach successfully worked and a large number of lead analogues were obtained in mostly quantitative yields. Now, we are writing to present the detail procedures for the library synthesis of 3-cyano-6-(2-hydroxyphenyl)pyridines by solid-phase combinatorial chemistry.

In order to immobilize one of the building components on polystyrene beads, 2-hydroxyacetophenone (3 equiv.) was reacted with brominated Wang resin (purchased from Nova Biochem) in the presence of K_2CO_3 (3 equiv.) in DMF at room temperature to give resin **1** in 92% yield. The reaction conditions of the following condensation with aldehydes (3 equiv.) and malononitrile (3 equiv.) were optimized as follows: The mixture was dissolved in 1,4-dioxane in a reaction vial (purchased from Wheaton, size 8 mL) and agitated at 80°C



Scheme 1.

Keywords: solid-phase synthesis; combinatorial chemistry; multi-component condensation; 3-cyanopyridine.

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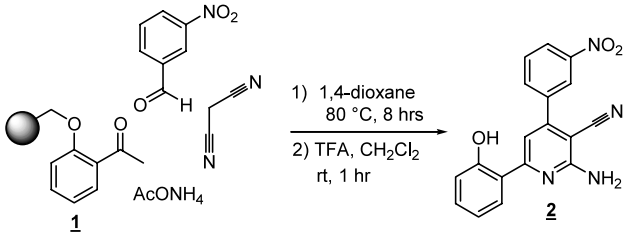


Scheme 2.

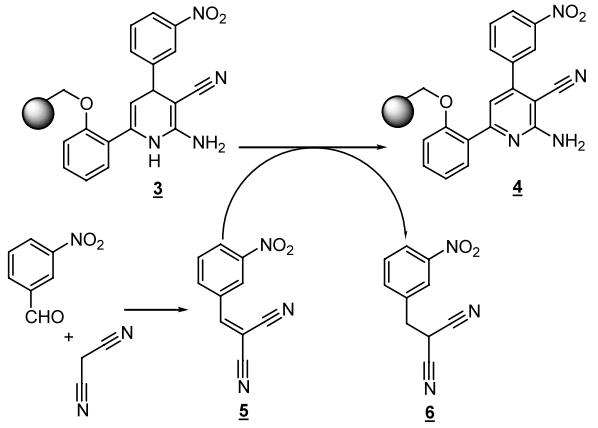


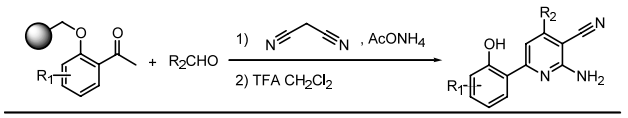
Figure 1.

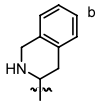
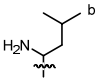
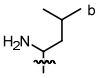
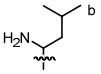
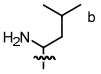
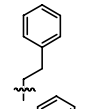
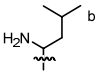
for 8 h in the presence of ammonium acetate (6 equiv.) with a screw cap. The resin was collected by filter and washed with dichloromethane and methanol, and followed by the cleavage reaction for 1 h at room temperature with 50% TFA in dichloromethane. When the solvent was removed off by evaporation, the target pyridine **2** was obtained as a TFA salt in 90% yield. HPLC analysis of the product gave a sole peak (>99% pure) (see: Scheme 2).

Since compound **6** was detected in the reaction mixture, it can be easily speculated that the excess amount of benzylidenemalononitrile **5** was initially synthesized by the Knoevenagel reaction between benzaldehyde and malononitrile and resulted in the oxidation of dihydropyridine **3**, that is theoretically possible product by this reaction (Fig. 1). Probably, this oxidation made the reaction be completed in excellent yield. The corresponding solution-phase reaction provided the target pyridine together with many byproducts, and its purification was quite laborious due to the complex mixture with poor solubility in usual organic solvents. This is one of the good examples that demonstrated the best use of inherent advantage of solid-phase chemistry, that allows us to use excess amount of reagents without any concern about their elimination from reaction mixtures after the completion of reactions.

In order to apply this reaction to a library synthesis, various kinds of acetophenones and aldehydes were subjected to give the corresponding 2-amino-3-cyanopyridines, and representative examples are shown

Table 1. Investigation of multi-component condensation on beads



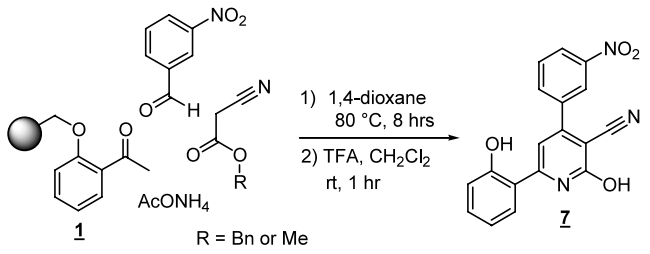
entry	R_1	R_2	Purity (%)[a]	entry	R_1	R_2	Purity (%)[a]
1	H		100	11	H		100
2	H		100	12	H		100
3	H		100	13	H		100
4	H		100	14	4-F		100
5	H		100	15	5-Me		100
6	H		63	16	5-MeO		100
7	H		100	17	3,4– $(CH_2)_3$ -		100
8	H		100	18	6-allyloxy		40
9	H		100				
10	H		100				

a) purities were estimated bsed on ELSD b) Boc-protected aminals were used.

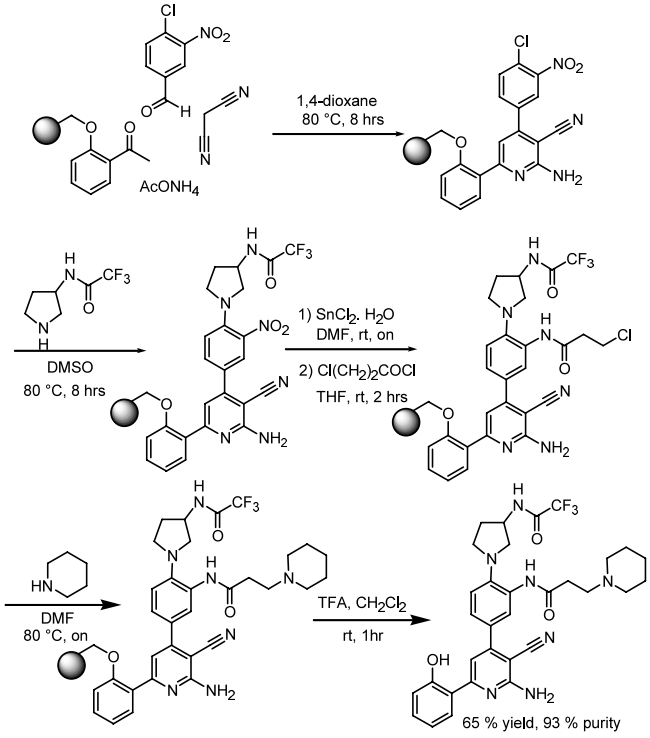
in Table 1. Almost all of the 2-hydroxyacetophenones gave expected pyridines in quantitative yields and purity, however, 2-hydroxy-6-allyloxyacetophenone (entry 18) proceeded together with many byproducts, perhaps due to the steric hindrance. For the aldehyde component, not only aromatic but also aliphatic aldehydes proceeded well (entries 6–17). This is a noteworthy example since there is only a few examples of 4-aliphatic pyridines synthesized by solid-phase chemistry.[2] Besides, both isovalel (entry 10) and 4-cyclohexyl (entry 11) pyridines were successfully obtained from the corresponding aldehydes, while such α-branched 4-alkyl moieties were often eliminated to give 4-unsubstituted pyridines in the oxidation stage.[12]

When benzyl cyanoacetate or methyl cyanoacetate was subjected instead of malononitrile, the corresponding 2-pyridone **7** was obtained in 73% yield (90% pure) (Scheme 3). This procedure can be applicable to a library synthesis of 3-cyano-2-hydroxypyridines and, further more, 2-alkylamino-3-cyanopyridines.[8]

Using 4-chloro-3-nitrobenzaldehyde, we performed very successful library synthesis as shown in Scheme 4. In this approach, the 4-chloro group was substituted with a variety of amines and the 3-nitro group was reduced with tin(II) chloride hydrate in DMF to allow us to



Scheme 3.



Scheme 4.

study another functional variation there . This successful event made us optimize the lead compound very quickly and this effective contribution took the pharmaceutical project to the advanced stage in a short period.[8]

In conclusion, an efficient solid-phase chemistry for the synthesis of 3-cyano-6-(2-hydroxyphenyl)pyridines by multi-component condensation was successfully established and a wide range of applications to the library synthesis of 3-cyanopyridines, including the pyridines with 4-aliphatic substitutions, was demonstrated. Since both purities and yields of this procedure were much better than those of the corresponding solution-phase, it was well demonstrated that inherent advantage of solid-phase chemistry to force the reactions that give poor yields in solution-phase chemistry into completion by using an excess of reagents. This procedure made worthwhile contributions to push on the combinatorial chemistry approach and bring one of our exploratory researches to the further advanced stage very quickly. In order to expand the range of applications, variation uses of the malononitrile component for the modification of 3-cyano group will be reported in due course.

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