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Synthesis of functionalized 1,2-dihydropyridines bearing quaternary carbon centers via an organocatalytic allylic alkylation

Gong-Feng Zou, Zhi-Peng Hu, Shi-Qiang Zhang, Wei-Wei Liao *

Department of Organic Chemistry, College of Chemistry, Jilin University, Changchun 130012, PR China

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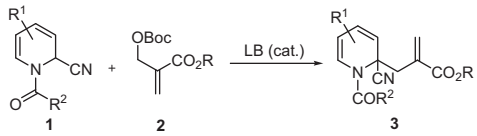
ABSTRACT

The first tertiary amine-catalyzed allylic alkylation of Reissert products of pyridine derivatives has been demonstrated. This protocol provided an efficient synthetic route for the construction of functionalized 2,2-disubstituted 1,2-dihydropyridines incorporating quaternary carbon centers with good to high regioselectivities and moderate enantioselectivities.

The syntheses of functionalized 1,2-dihydropyridines have received considerable attention due to their importance in organic synthesis and medicinal chemistry.[1] For example, 1,2-dihydropyridines are important building blocks in the preparation of piperidine scaffolds which are valuable and prevalent heterocyclic structural units in biologically active compounds and in medicines which have been enormously important in treating diseases.[2] Although a number of synthetic methods have been developed to construct these valuable structural motifs,[1,3] few examples have been demonstrated to prepare the functionalized 1,2-dihydropyridines incorporating quaternary carbon centers.[4,5]

Reissert reaction of pyridine derivatives has been well known to construct α-cyano substituted 1,2-dihydropyridines which can be regarded as cyclic α-aminonitriles for several decades.[6] In contrast to other α-aminonitriles bearing a α-hydrogen which are exceptionally versatile intermediates in synthetic chemistry and have been widely used in the generation of multiple polyfunctional structures,[7] the synthetic applications of dihydropyridines derived from Reissert reaction of pyridine derivatives have received less attention.[1a] With the goal of developing efficient metal-free processes to construct the diverse carbon frameworks incorporating quaternary carbon centers,[8] herein we report a facile approach to prepare 2,2-disubstituted functionalized dihydropyridines bearing quaternary carbon centers from Reissert products of pyridine derivatives by using a Lewis base assisted Brønsted base catalyzed allylic alkylation,[9] which takes advantage of the powerful anion-stabilizing capacity of the cyano-group (Scheme 1).



Scheme 1. Synthetic strategy on preparation of 2,2-disubstituted functionalized dihydropyridines. LB = Lewis base.

Our initial investigation commenced with Morita–Baylis–Hillman (MBH) adduct **2** and ethyl 2-cyano-5-(diisopropylcarbamoyl) pyridine-1(2*H*)-carboxylate **1aa** which are readily prepared from Reissert reaction of nicotinic amide. In the presence of catalytic amount of DABCO (20 mol %), the reaction provided the desired α-selective alkylation product **3a** along with the small amount of γ-regioisomer **4aa** in CH_3CN (Table 1, entry 1). Other tertiary amine catalysts such as DMAP and DBU have been examined, and the reactions afforded the desired product **3aa** in reduced yields (Table 1, entries 2–3). Similar to DMAP and DBU, treatment of **1aa** and **2** with PPh_3 (10 mol %) gave alkylation product **3aa** in moderate yield and regioisomer **4aa** in 16% yield (Table 1, entry 4). Further screening on solvents showed that the α-selective allylic alkylation reaction proceeded well in more polar solvent and gave the desired product **3aa** in good yields (Table 1, entries 1 and 8), while the moderate yields were obtained in the presence of less polar solvents due to the increased production of regioisomer **4aa** (Table 1, entries 5–7).

* Corresponding author.
E-mail address: wliao@jlu.edu.cn (W.-W. Liao).

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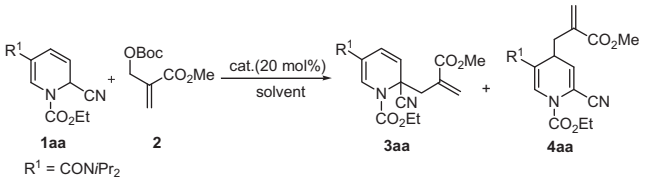
Table 1
Optimization of allylic alkylation of compound **1a** with MBH carbonate **2**[a]

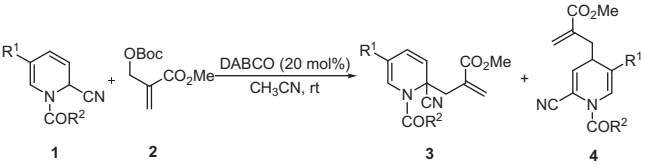


Entry	Cat.	Solvent	Yield[b] (%)	**3aa**/**4aa**[c]
1	DABCO	CH_3CN	82	9.1:1
2	DMAP	CH_3CN	61	10:1
3	DBU	CH_3CN	50	5.6:1
4	PPh_3	CH_3CN	50	3.1:1
5	DABCO	$PhCH_3$	62	2/1
6	DABCO	DCM	66	2/1
7	DABCO	THF	66	2.8/1
8	DABCO	DMF	77	7/1

[a] Reactions were performed with **1aa** (0.2 mmol), **2** (0.26 mmol), and catalyst (20 mol %) at 30 °C in solvent (*c* = 0.2 M).
[b] Yield of isolated product **3aa**.
[c] Based on ^{1}H NMR analysis.

With these optimized reaction conditions in hand, allylic alkylation reactions between 1,2-dihydropyridines **1** bearing various substituents at the 5-postion with MBH adduct **2** were evaluated firstly (Table 2). The substrates with amide moieties as electron-withdrawing groups (EWG) were well tolerant. The range of nicotinic amide Reissert compounds furnished the desired 2,2-disubstituted dihydropyridines **3** in good to high yields with moderate to high regioselectivities (Table 2, entries 1-5). Notably, substrate **1ac** including the Weinreb amide moiety was a suitable substrate and gave the desired product **3ac** in good yield with good regioselectivity (Table 1, entry 3), which enabled the further elaborate synthetic transformation. In addition, substrates with substituents such as cyano and ester at the 5-postion also gave the α-selective alkylation products **3** in good yields (Table 2, entries 6–7). *N*Substituents on 1,2-dihydropyridines **1** were examined. *N*-Isobutyloxy

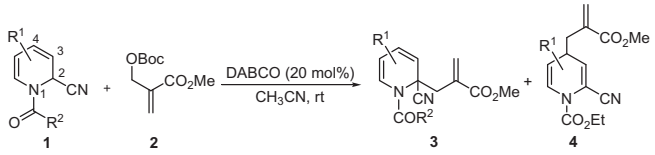
Table 2
Allylic alkylation of MBH adduct **2** with 1,2-dihydropyridines **1** with substituents at 5-position[a]



Entry	R^1	R^2	**1**	Yield[b] (%)	**3**/**4**[c]
1	$CON(iPr)_2$	OEt	**1aa**	82 (**3aa**)	9.1/1
2	$CONEt_2$	OEt	**1ab**	77 (**3ab**)	8.5/1
3	CON(OMe)Me	OEt	**1ac**	70 (**3ac**)	9/1
4	$CON(CH_2)_5$	OEt	**1ad**	78 (**3ad**)	11/1
5[d]	$CON(CH_2)_4O$	OEt	**1ae**	77 (**3ae**)	10/1
6[d]	CO_2Me	OEt	**1af**	99 (**3af**)	8/1
7[d,e]	CN	OEt	**1ag**	80 (**3ag**)	17/1
8	$CON(CH_2)_4O$	O*i*-Bu	**1ah**	72 (**3ah**)	9/1
9	$CON(CH_2)_4O$	OBn	**1ai**	61 (**3ai**)	13/1
10	$CON(CH_2)_4O$	OPh	**1ag**	59 (**3aj**)	>19/1
11	CO_2Me	Me	**1ak**	71 (**3ak**)	2.7/1

[a] Reactions were performed with **1** (0.2 mmol), **2** (0.26 mmol), and DABCO (20 mol %) at 30 °C in CH_3CN (*c* = 0.2 M) for 1–5 h.
[b] Yield of isolated product.
[c] Determined by ^{1}H NMR analysis.
[d] Unseparated mixture was isolated.
[e] 4 Å molecular sieve was added.

Table 3
Allylic alkylation of MBH adduct **2** with 1,2-dihydropyridines **1** with substituents at the 4 or 3-position[a]



Entry	R^1	R^2	**1**	*t* (h)	Yield[b] (%)	**3**/**4**[c]
1	(4-)$CON(Et)_2$	OEt	**1ba**	13	66 (**3ba**)	2.3/1
2	(3-)$CON(Et)_2$	OEt	**1ca**	39	59 (**3ca**)	—[d]
3	(4-)CON(OMe)Me	OEt	**1bb**	13	70 (**3bb**)	5.3/1
4[e]	(3-)CON(OMe)Me	OEt	**1cb**	24	63 (**3cb**)	—[d]
5	(4-)$CON(iPr)_2$	OEt	**1bc**	11	66 (**3bc**)	3.7/1
6	(3-)$CON(iPr)_2$	OEt	**1cc**	24	nr	—[d]
7	(4-)$CON(CH_2)_4O$	OEt	**1bd**	3	54 (**3bd**)	1.9/1
8	(3-)$CON(CH_2)_4O$	OEt	**1cd**	24	60 (**3cd**)	—[d]
9	(4-)$CON(CH_2)_5$	OEt	**1be**	3	66 (**3be**)	2.7/1
10[e]	(3-)$CON(CH_2)_5$	OEt	**1ce**	24	57 (**3ce**)	—[d]
11	(4-)CO_2Me	OEt	**1bf**	24	nr	
12[e]	(3-)CO_2Me	OEt	**1cf**	22	48 (**3cf**)	—[d]
13[f]	(4-)CN	OEt	**1bg**	4	28 (**3bg**)	—[d]
14[f]	(3-)CN	OEt	**1cg**	5	97 (**3cg**)	—[d]
15[e]	(4-)Cl	OEt	**1bh**	24	77 (**3bh**)	—[d]
16	(3-)Cl	OEt	**1ch**	5	76 (**3ch**)	—[d]
17	(4-)CO_2Me	Me	**1bi**	24	nr	—
18	(3-)CO_2Me	Me	**1ci**	23	66 (**3ci**)	—[d]
19	(4-)CO_2Me	Ph	**1bj**	24	nr	—
20	(3-)CO_2Me	Ph	**1cj**	24	75 (**3cj**)	—[d]

[a] Reactions were performed with **1** (0.2 mmol), **2a** (0.26 mmol), and DABCO (20 mol %) at 30 °C in CH_3CN (*c* = 0.2 M).
[b] Yield of isolated product.
[c] Determined by ^{1}H NMR analysis.
[d] No compound **4** was detected.
[e] Performed at 60 °C.
[f] 4 Å molecular sieve was added.

Reissert analogue **1ah** gave the similar result as that of *N*-ethoxycarbonyl substituted 1,2-dihydropyridine **1aa** (Table 2, entry 8), while *N*-benzyloxycarbonyl and *N*-phenyloxycarbonyl Reissert analogues provided the desired products **3ag**–**3ak** in decreased yields with high regioselectivities (Table 2, entries 9–10). Besides, *N*-acetyl 1,2-dihydropyridine **1ak** also served as suitable substrate and gave product **3ak** in moderate yield with low regioselectivity (Table 2, entry 11).

On the basis of these, the number of 1,2-dihydropyridines **1** with substituents at the 4- and 3-position were investigated, respectively. The results are illustrated in Table 3. In general, the reaction of substrate **1** with amide moiety at the 4-position proceeded faster than that of substrate **1** with amide moiety at the 3-position which required prolonged reaction time, presumably due to the steric hindrance effects of the R^1 group at the 3-position. Treatment of 1,2-dihydropyridine **1cc** with bulk substituent at the 3-position failed to give the desired product **3cc** (Table 3, entry 6), while analogue **1bc** with bulk substituent at the 4-position furnished the allylic alkylation product **3bc** in moderate yield (Table 3, entry 5), which is consistent with aforementioned hypothesis. Substrates (**1bb** and **1cb**) possessing Weinreb amide moieties can also be employed and gave the desired products in good yields irrespective of the substitution patterns (Table 3, entries 3–4). Further investigations on the reactions of substrates **1** bearing other electron-withdrawing groups (R^1) revealed that the substitution patterns and the electronic properties (R^1) have considerable influence on the chemical conversion and regioselectivity of the developed process. For examples, substrates (**1cf** and **1cg**) with ester or cyano moieties (R^1) at the 3-position provided the desired products in moderate to good yields (Table 3, entries 12 and 14), while corresponding 1,2-dihydropyridines (**1bf** and **1bg**) with R^1