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SYNTHESIS OF 4-SUBSTITUTED-PYRIDINE-2,6-DICARBOXYLIC ACID DERIVATIVES FROM PYRUVATES AND ALDEHYDES IN ONE POT

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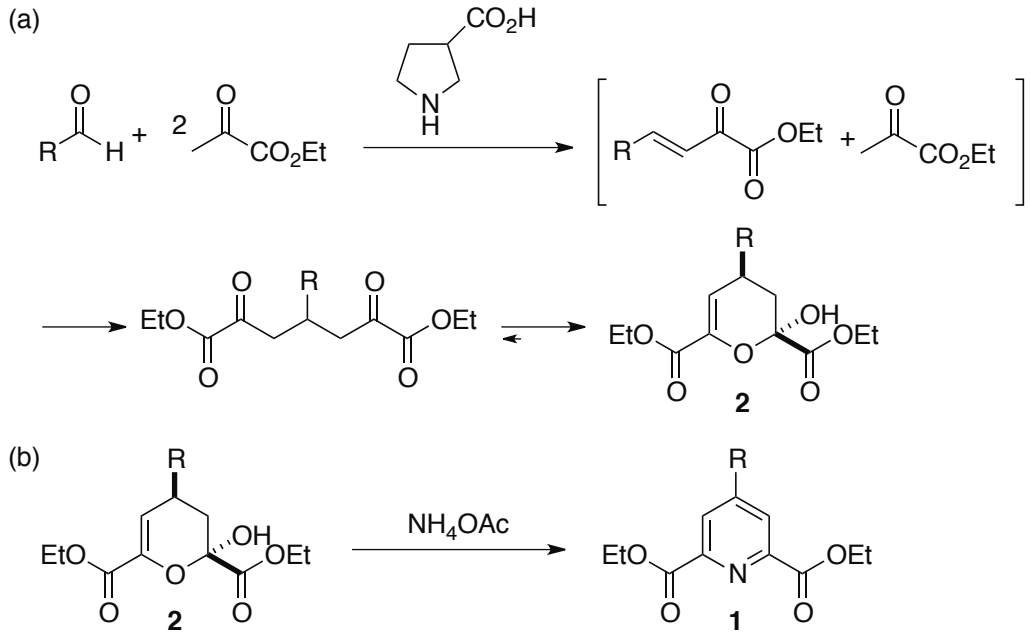
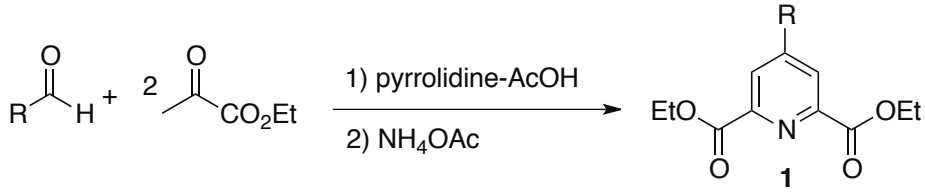
Abstract – 4-Substituted-pyridine-2,6-dicarboxylic acid derivatives were synthesized in one pot under mild conditions via the formation of dihydropyran derivatives from pyruvates and aldehydes catalyzed by pyrrolidine-acetic acid, followed by the reaction with ammonium acetate.

Pyridine-2,6-dicarboxylic acids (or dipicolinic acids) and their derivatives are used as ligands for metals, small molecules, and biomolecules.[1] They have also been used as building blocks for the synthesis of biofunctional molecules, probes for visualization of cells and molecules of interest, and solid-support reagents.[1] Previously reported methods for the synthesis of substituted pyridine-2,6-dicarboxylic acid derivatives often require long routes and severe conditions.[1,2] Concise methods for the synthesis of substituted pyridine-2,6-dicarboxylic acid derivatives under mild conditions would be beneficial. We have recently developed a concise method for the synthesis of 4-substituted-pyridine-2,6-dicarboxylic acid derivatives **1** (Scheme 1).[3] In the method, pyruvates and aldehydes are used as the starting materials to firstly afford functionalized dihydropyran derivatives **2** in cascade reactions in one pot under β-proline catalysis (Scheme 1a), which are then transformed to 4-substituted-pyridine-2,6-dicarboxylic acid derivatives **1** (Scheme 1b).[3] Dihydropyran derivatives **2** were also transformed to various molecules including amino group-substituted dihydropyrans, amino acid derivatives, dihydrodiazepines, and quinoxalinone derivatives.[3] Here we report the development of a one-pot version of the synthesis of 4-substituted-pyridine-2,6-dicarboxylic acid derivatives **1** starting from pyruvates and aldehydes with pyrrolidine-acetic acid catalysis (Scheme 2).



Scheme 1. Our previous synthesis of 4-substituted-pyridine-2,6-dicarboxylic acid derivatives **1**[3]

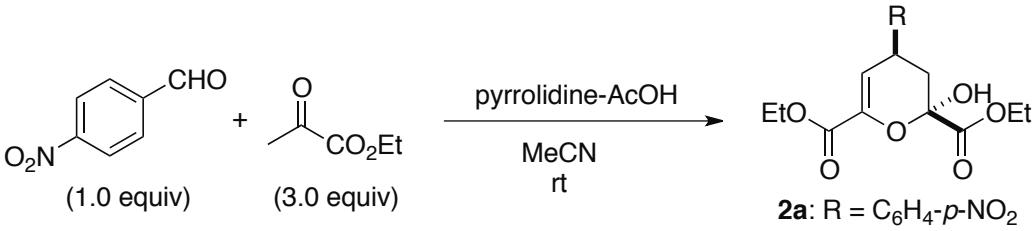


Scheme 2. One-pot synthesis of 4-substituted-pyridine-2,6-dicarboxylic acid derivatives **1** developed in this study

In our previous two-pot method to synthesize **1**, functionalized dihydropyran derivatives **2** were synthesized from pyruvates and aldehydes under β-proline catalysis.[3] It has been recognized that reactions of simple pyruvates (such as ethyl pyruvate and methyl pyruvate) as nucleophiles (i.e., reactions of enolates and enamines of pyruvates) with other electrophiles are often difficult, and examples of these reactions have been limited.[4,5] Self-condensation of simple pyruvates often occurs even in the presence of other electrophiles.[3,4] In our β-proline-catalyzed reactions of pyruvates with aldehydes, pyruvates acted as nucleophiles to lead the dihydropyran derivatives.[3] Whereas β-proline was the best catalyst among those tested for the formation of dihydropyran derivatives **2**, other amino acids (such as (*S*)-alanine and β-alanine) and amines (such as Et_3N and DBU) did not work as the catalyst for the reaction to give **2**.[3] When pyrrolidine-acetic acid was used as the catalyst, the desired dihydropyran derivative was formed although the yield was low under the previously tested conditions.[3] Because pyrrolidine and acetic acid are more readily accessed or obtained than β-proline, we first searched for

suitable conditions for the synthesis of **2a** using pyrrolidine and acetic acid as catalyst components (Table 1) toward the development of the one-pot methods. The use of higher loadings of acetic acid relative to pyrrolidine above a certain level was favored for the formation of **2a** (Table 2, entries 4-7), but further high loading of acetic acid did not improve the yield of **2a** (Table 1, entry 7 versus entry 8). With appropriate loadings of pyrrolidine and acetic acid as the catalyst, dihydropyran derivative **2a** was obtained in reasonable yields. As shown in Table 1, entry 7, the reaction of the aldehyde (1.0 equiv) and ethyl pyruvate (3.0 equiv) using pyrrolidine (0.4 equiv) and acetic acid (1.0 equiv) as the catalyst resulted in the best yield of **2a** among the conditions tested.

Table 1. Optimizations of the pyrrolidine-acetic acid catalysis in the reaction to form **2a**[a]



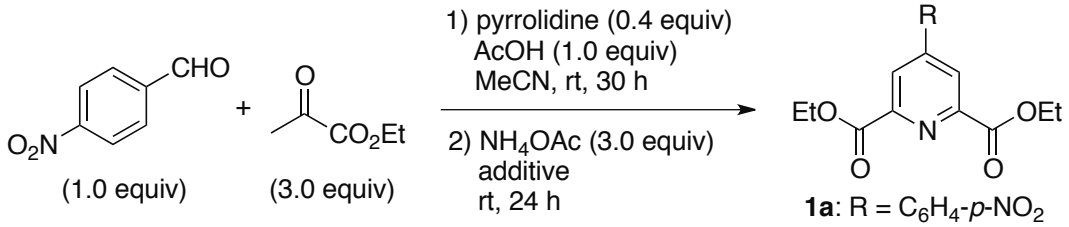
Entry	Pyrrolidine (equiv)	AcOH (equiv)	Time (h)	Yield (%)[b]
1[c]	0.1	-	48	4
2[c]	0.1	0.1	48	27
3[c]	-	0.1	48	nd
4	0.2	0.2	24	37
5	0.2	0.4	24	38
6	0.2	1.0	24	49
7	**0.4**	**1.0**	**24**	**61**
8	0.4	2.0	24	60
9	0.5	1.0	24	59
10	0.5	2.0	24	57

[a] Reaction conditions: *p*-nitrobenzaldehyde (0.5 mmol, 1.0 equiv), ethyl pyruvate (1.5 mmol, 3.0 equiv), and indicated loadings of pyrrolidine and acetic acid in MeCN (0.5 mL) at 25 °C except where indicated. [b] Isolated yield (the cyclic form and the linear form were combined); nd = formation of **2a** was not detected by TLC analyses. [c] Reaction using *p*-nitrobenzaldehyde (1.0 mmol, 1.0 equiv) and ethyl pyruvate (2.2 mmol, 2.2 equiv) in MeCN (1.0 mL); taken from our previous paper.[3]

In the reaction using pyrrolidine and acetic acid (1:1) as the catalyst (Table 1, entries 2 and 4), pyruvate self-condensation products were observed. Slightly acidic conditions in the presence of pyrrolidine (i.e., conditions with higher loadings of acetic acid than pyrrolidine, such as Table 1, entry 7) favored the formation of **2a** over the pyruvate self-condensation.

In our previous study, addition of pyrrolidine to the solution of **2a** in CD_3CN resulted in the decomposition of **2a** and in the formation of a complex mixture.[3] Treatment of **2a** in CD_3CN with Et_3N also resulted in slow decomposition of **2a**.[3] In contrast, addition of acetic acid to the solution of **2a** in CD_3CN did not lead notable decomposition of **2a** after 1 day.[3] The slightly acidic conditions resulting from the higher loading of acetic acid than pyrrolidine may also prevent the decomposition of the generated product **2a**.

Table 2. Optimizations of the second-step conditions to form **1a** in one pot[a]



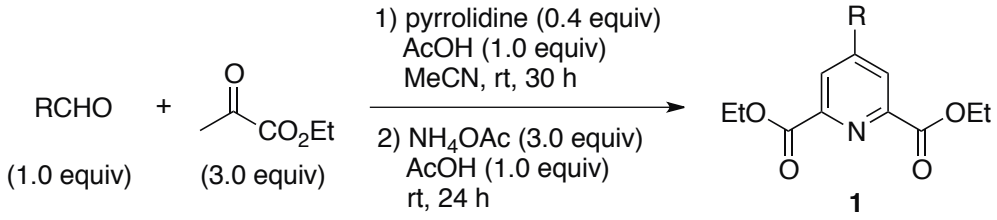
Entry	Additive (equiv)	Yield (%)[b]
1	-	50
2	Et_3N (1.0 equiv)	50
3	**AcOH (1.0 equiv)**	**68**
4[c]	-	46

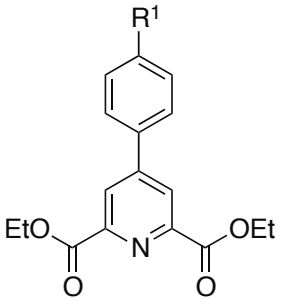
[a] Reaction was performed using *p*-nitrobenzaldehyde (1.0 mmol, 1.0 equiv) and ethyl pyruvate (3.0 mmol, 3.0 equiv) in the presence of pyrrolidine (0.4 mmol, 0.4 equiv) and acetic acid (1.0 mmol, 1.0 equiv) in MeCN (1.0 mL) at 25 °C for 30 h, followed by addition of NH_4OAc (3.0 mmol, 3.0 equiv) except where indicated and additive (if added) and by being stirred at the same temperature for 24 h. [b] Isolated yield. [c] NH_4OH was used instead of NH_4OAc.

Next, we optimized the conditions to enable the synthesis of pyridine derivative **1a** in one pot (Table 2) by adapting the best conditions identified to form **2a** (Table 1, entry 7). We found that addition of acetic acid in the second step improved the yield of the pyridine derivative (Table 2, entry 3 versus entry 1). The use of acetic acid at the pyridine formation stage may act to retain or to provide an acidic environment in the presence of NH_4OAc, minimizing the decomposition of **2a**, activating **2a** by protonation to trigger the addition reaction of NH_4OAc, and accelerating the cyclization of the intermediate and the elimination of water to lead the formation of **1a**. The one-pot method yielded **1a** in 68% (Table 2, entry 3); this was a better result than that of our previous two-step route with the β-proline catalysis (Scheme 1), in which the yield of **1a** was 56% from the aldehyde and pyruvate, based on the calculation of 72% for the first pot to give **2a** and 78% for the second pot to generate **1a** from **2a**.[3] The yield of **1a** in the one-pot method (Table 2, entry 3) was also higher than the isolated yield of **2a** in Table

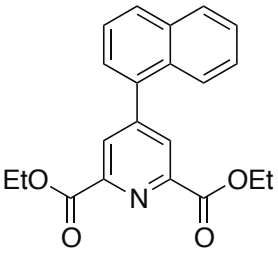
1, entry 7. The one-pot procedure bypasses the purification of dihydropyran derivatives **2**, which is often difficult because of the equilibrium between the cyclic form and the linear form (Scheme 1a).

Table 3. Synthesis of various 4-substituted-pyridine-2,6-dicarboxylic acid derivatives from aldehydes and pyruvate[a]

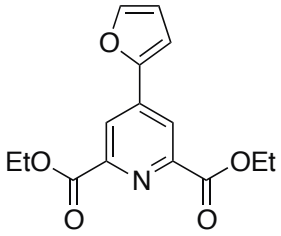




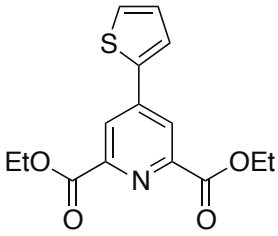
1a: $R^1 = NO_2$ 68%
(72% x 78% = 56%)[b]
1b: R^1 = Cl 63%
(64% x 69% = 44%)[b]
1c: R^1 = Br 57%
(65% x 75% = 49%)[b]
1d: R^1 = F 53%
1e: $R^1 = CF_3$ 51%
1f: R^1 = CN 66%
1g: R^1 = C≡CH 46%



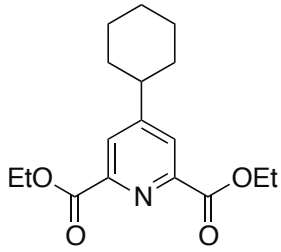
1h 48%



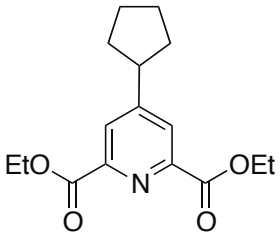
1i 39%
(51% x 79% = 40%)[b]



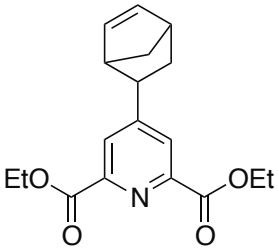
1j 48%



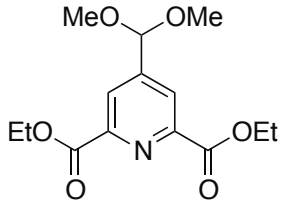
1k 35%
(64% x 72% = 46%)[b]



1l 35%



1m 41%



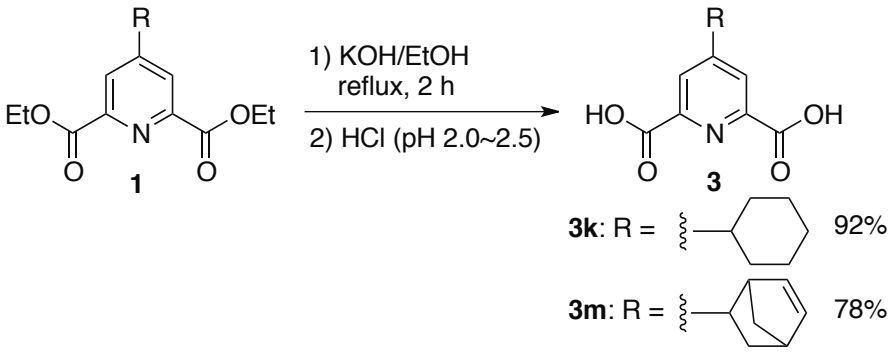
1n 71%
(88% x 67% = 59%)[b]

[a] Reaction was performed using aldehyde (1.0 mmol) and ethyl pyruvate (3.0 mmol) in the presence of pyrrolidine (0.4 mmol) and acetic acid (1.0 mmol) in MeCN (1.0 mL) at 25 °C for 30 h, followed by addition of NH_4OAc (3.0 mmol) and acetic acid (1.0 mmol) and by being stirred at the same temperature for 24 h. [b] Data of the two-pot reactions; yield of the formation of **2** using the β-proline catalysis (Scheme 1a),[3] yield of **1** from **2** (Scheme 1b),[3] and yield of **1** calculated from the aldehyde.

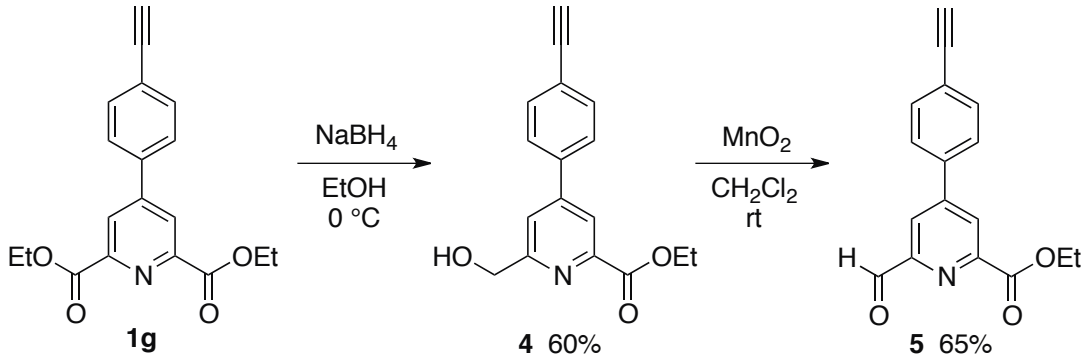
With the conditions identified, various 4-substituted-pyridine-2,6-dicarboxylic acid derivatives **1a**-**1n** were synthesized in one pot (Table 3). Reactions using substituted benzaldehydes, naphthaldehyde, aryl

aldehydes, α-branched alkyl aldehydes, and α,α-dimethoxyacetaldehyde all afforded the pyridine derivatives. For the pyridine derivatives that were previously synthesized using our two pot procedures, the calculated yields are also indicated. In most cases, the one-pot method yield was higher than our previous two-pot yield.[6] The one-pot method was readily scaled: Pyridine-2,6-dicarboxylic acid derivative **1g** (0.73 g) was obtained in 45% in one pot starting from 5.0 mmol aldehyde.

Pyridine-2,6-dicarboxylic acid derivatives are often used as acids.[1,2] The ester group of **1** is also a useful site to introduce an alcohol or aldehyde functional group. To demonstrate the utility of our one-pot synthesis, diesters **1k** and **1m** were hydrolyzed to afford the corresponding diacid derivatives **3k** and **3m** (Scheme 3). Pyridine derivatives **4** and **5** were also obtained by transformations of one ester group of the diester derivative (Scheme 4).



Scheme 3. Hydrolysis of **1** to afford 4-substituted-pyridine-2,6-dicarboxylic acids **3**



Scheme 4. Transformations to lead to pyridine derivatives **4** and **5**

In conclusion, we have developed one pot reactions for the synthesis of 4-substituted-pyridine-2,6-dicarboxylic acid derivatives from pyruvates and aldehydes under mild conditions. Various derivatives were synthesized using our concise, atom-economical method. The

developed reaction method should be useful for the synthesis of 4-substituted-pyridine-2,6-dicarboxylic acid derivatives that are of interest as ligands, bioactives, and their building blocks.

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Supporting Information Available: Experimental procedures, product characterization, and NMR spectra.

REFERENCES AND NOTES

1. A. Picot, A. D'Aleo, P. L. Baldeck, A. Grichine, A. Duperray, C. Andraud, and O. Maury, *J. Am. Chem. Soc*., 2008, **130**, 1532; X.-C. Su, B. Man, S. Beeren, H. Liang, S. Simonsen, C. Schmitz, T. Huber, B. A. Messerle, and G. Otting, *J. Am. Chem. Soc*., 2008, **130**, 10486; A. T. Parsons and J. S. Johnson, *J. Am. Chem. Soc*., 2009, **131**, 3122; J. Li, K. B. Pilla, Q. Li, Z. Zhang, X. Su, T. Huber, and J. Yang, *J. Am. Chem. Soc*., 2013, **135**, 8294; C. J. van Staveren, V. M. L. J. Aart, P. D. J. Grootenhuis, W. J. H. Droppers, J. van Eerden, S. Harkema, and D. N. Reinhoudt, *J. Am. Chem. Soc*., 1988, **110**, 8134; R. Tang, Q. Zhao, Z. Yan, and Y. Luo, *Synth. Commun*., 2006, **36**, 2027; D. Wang, P. Y. Zavalij, and A. N. Vedernikov, *Organometallics*, 2013, **32**, 4882; L. L. Zhu, T. Kawate, X. Liu, Y. B. Kim, Y. Zhao, G. Feng, J. Banerji, H. Nash, C. Whitehurst, S. Jindal, A. Siddiqui, B. Seed, and J. L. Wolfe, *Bioorg. Med. Chem*., 2012, **20**, 750; L. F. Silvian, J. E. Friedman, K. Strauch, T. G. Cachero, E. S. Day, F. Qian, B. Cunningham, A. Fung, L. Sun, L. Su, Z. Zheng, G. Kumaravel, and A. Whitty, *ACS Chem. Biol*., 2011, **6**, 636; P. Hommes, C. Fischer, C. Lindner, H. Zipse, and H.-U. Ressing, *Angew. Chem. Int. Ed*., 2014, **53**, 7647; D. S. Kopchuk, N. V. Chepchugov, G. A. Kim, G. V. Zyryanov, I. S. Kovalev, V. L. Rusinov, and O. N. Chupakhin, *Tetrahedron Lett*., 2016, **57**, 296.
2. G. Labbe, A. P. Krismanich, S. de Groot, T. Rasmusson, M. Shang, M. D. R. Brown, G. I. Dmitrienko, and J. G. Guillemette, *J. Inorg. Biochem*., 2012, **112**, 49; R. Shelkov and A. Melman, *Eur. J. Org. Chem*., 2005, 1397.
3. P. V. Chouthaiwale and F. Tanaka, *Chem. Commun*., 2014, **50**, 14881.
4. P. Dambruoso, A. Masai, and A. Dondoni, *Org. Lett*., 2005, **7**, 4657; K. Juhl, N. Gathergood, and K.

A. Jorgensen, *Chem. Commun.*, 2000, 2211; H. Torii, M. Nakadai, K. Ishihara, S. Saito, and H. Yamamoto, *Angew. Chem. Int. Ed.*, 2004, **43**, 1983; O. El-Sepelgy and J. Mlynarski, *Adv. Synth. Catal.*, 2013, **355**, 281; K. Juhl, N. Gathergood, and K. A. Jorgensen, *Angew. Chem. Int. Ed.*, 2001, **40**, 2995; M. Raj, G. S. Parashari, and V. K. Singh, *Adv. Synth. Catal.*, 2009, **351**, 1284; C. Luo and Y. Huang, *J. Am. Chem. Soc.*, 2013, **135**, 8193; J.-M. Vincent, C. Margottin, M. Berlande, D. Cavagnat, T. Buffeteau, and Y. Landais, *Chem. Commun.*, 2007, 4782.

5. Because of the difficulty in control of the nucleophilic and electrophilic reactivities of pyruvates, pyruvate surrogates and precursors have often been used: D. Enders and T. Gasperi, *Chem. Commun.*, 2007, 88; R. Winzar, J. Philip, and M. J. Kiefel, *Synlett*, 2010, 583.
6. During the synthesis of **1n**, formation of the corresponding 1,4-dihydropyridine derivative was observed, which was readily oxidized under air to give **1n**.