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# Titanium-Mediated Spirocyclization Reactions of 4-Alkylpyridines

**Sharavathi G. Parameswarappa and F. Christopher Pigge***

*Department of Chemistry, University of Iowa, Iowa City, Iowa 52242*

*chris-pigge@uiowa.edu*

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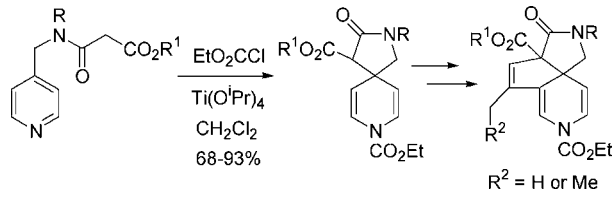
## ABSTRACT




**Pyridines substituted at the 4-position with alkyl tethers containing β-dicarbonyl moieties were converted to spirocyclic 4,4-disubstituted dihydropyridines. Optimal conditions for these transformations involved N-acylation of the pyridine substrate with a chloroformate electrophile in the presence of $Ti(O^iPr)_4$. Cyclization products could be easily converted into spiro-piperidine derivatives or elaborated into more complex heterocyclic frameworks via Au-catalyzed cycloisomerization.**

Elaboration of pyridine ring systems offers convenient access to a wealth of substituted aza-heterocyclic derivatives. In particular, *inter*molecular addition of nucleophiles to activated *N*-alkyl- or *N*-acylpyridinium cations is well-established, and the resulting 1,2- or 1,4-dihydropyridine products can be converted into substituted piperidines, pyridines, and other heterocyclic ring systems.[1] In contrast, construction of polycyclic heterocyclic frameworks via *intra*molecular nucleophilic additions to pyridines or pyridinium salts is much less common.[2] Importantly, such reaction manifolds provide concise entry to fused-ring and/or spirocyclic dihydropyridine derivatives that are well-suited for further synthetic manipulation.[3] Moreover, spiropiperidine-based ring systems are encountered in numerous bioactive materials of potential pharmacological significance.[4] Consequently, further expansion of intramolecular reaction pathways available to substituted pyridines (particularly those leading to spiro-dihydropyridine products) is of general interest to the synthetic and medicinal chemistry communities.

Most spirocyclization reactions involving pyridine substrates are initiated by alkylation or acylation of the pyridyl nitrogen to afford electrophilic pyridinium cation intermedi-

(1) For recent examples of intermolecular nucleophilic additions to activated pyridines, see: (a) McCall, W. S.; Grillo, T. A.; Comins, D. L. *J. Org. Chem.* **2008**, *73*, 9744. (b) Gotchev, D. B.; Comins, D. L. *J. Org. Chem.* **2006**, *71*, 9393. (c) Comins, D. L.; Sahn, J. J. *Org. Lett.* **2005**, *7*, 5227. (d) Lemire, A.; Charette, A. B. *J. Org. Chem.* **2010**, *75*, 2077. (e) Barbe, G.; Pelletier, G.; Charette, A. B. *Org. Lett.* **2009**, *11*, 3398. (f) Larivée, A.; Charette, A. B. *Org. Lett.* **2006**, *8*, 3955. (g) Focken, T.; Charette, A. B. *Org. Lett.* **2006**, *8*, 2985. (h) Andersson, H.; Banchelin, T. S.-C.; Das, S.; Olsson, R.; Almqvist, F. *Chem. Commun.* **2010**, *46*, 3384. (i) Donohoe, T. J.; Connolly, M. J.; Walton, L. *Org. Lett.* **2009**, *11*, 5562. (j) Fernández-Ibáñez, M. A.; Maciá, B.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 9339. (k) Yamada, S.; Inoue, M. *Org. Lett.* **2007**, *9*, 1477.

(2) For examples of intramolecular nucleophilic additions to pyridines leading to spiro-dihydropyridine products, see: (a) Brice, H.; Clayden, J. *Chem. Commun.* **2009**, 1964. (b) Arnott, G.; Brice, H.; Clayden, J.; Blaney, E. *Org. Lett.* **2008**, *10*, 3089. (c) Arnott, G.; Clayden, J.; Hamilton, S. D. *Org. Lett.* **2006**, *8*, 5325. (d) Goldmann, S.; Born, L.; Kazda, S.; Pittel, B.; Schramm, M. *J. Med. Chem.* **1990**, *33*, 1413. (e) Weller, D. D.; Stirchak, E. P.; Weller, D. L. *J. Org. Chem.* **1983**, *48*, 4597.

(3) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141.

(4) (a) Wang, J.; Cady, S. D.; Balannik, V.; Pinto, L. H.; DeGrado, W. F.; Hong, M. *J. Am. Chem. Soc.* **2009**, *131*, 8066. (b) Methot, J. L.; Hamblett, C. L.; Mamprien, D. M.; Jong, J.; Harsch, A.; Szewczak, A. A.; Dahlberg, W. K.; Middleton, R. E.; Hughes, B.; Fleming, J. C.; Wang, H.; Kral, A. M.; Ozerova, N.; Cruz, J. C.; Haines, B.; Chenard, M.; Kenific, C. M.; Secrist, J. P.; Miller, T. A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6104. (c) Xiao, D.; Palani, A.; Aslanian, R.; McKittrick, B. A.; McPhail, A. T.; Correll, C. C.; Phelps, P. T.; Anthes, J. C.; Rindgen, D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 783. (d) Oberdorf, C.; Schepmann, D.; Vela, J. M.; Diaz, J. L.; Holenz, J.; Wünsch, B. *J. Med. Chem.* **2008**, *51*, 6531. (e) Bienaymé, H.; Chêne, L.; Grisoni, S.; Grondin, A.; Kaloun, E.-B.; Poigny, S.; Rahali, H.; Tam, E. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4830. (f) Bondensgaard, K.; Ankersen, M.; Thøgersen, H.; Hansen, B. S.; Wulff, B. S.; Bywater, R. P. *J. Med. Chem.* **2004**, *47*, 888. (g) Kazmierski, W. M.; Furfine, E.; Spaltenstein, A.; Wright, L. L. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3431.

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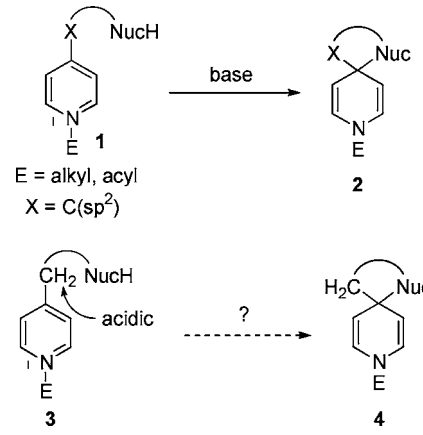
**Scheme 1**



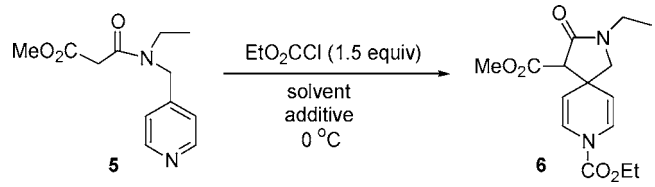

ates (**1**, Scheme 1). Prior attachment of a nucleophilic group to C4 of the pyridine ring can then result in cyclization to afford spiro-dihydropyridines **2**.[2a−c,e] Notably, reported transformations of this type have all utilized pyridyl derivatives that do not possess benzylic hydrogens (i.e., X = C($sp^2$) as in carbonyl or aryl groups). While this feature removes concerns over unwanted deprotonation events arising from the increased acidity exhibited by C4 benzylic hydrogens upon pyridine N-alkylation or N-acylation, it also narrows the scope of the spirocyclization process. Thus, we became interested in exploring the feasibility of converting pyridinium electrophiles **3** (possessing C4 alkyl substituents) to spiro adducts **4** through cyclization with appropriate tethered nucleophiles. In turn, functionality inherent to dihydropyridines **4** should render these products versatile synthetic intermediates useful for construction of more elaborate heterocyclic frameworks.

At the outset, we reasoned that strongly basic reaction environments would be incompatible with substrates such as **3** due to formation of anhydrobases via benzylic deprotonation.[5] Hence, nucleophilic addition would need to proceed under near neutral or acidic conditions. Consequently, we opted to attach stabilized pro-nucleophiles (i.e., $\beta$-dicarbonyls) to our pyridine substrates, and a particularly convenient class of cyclization precursor (**5**) was easily prepared by treatment of commerically available 4-(ethylaminomethyl)pyridine with dimethyl malonate.

Pyridine derivative **5** was employed for initial screening of reaction conditions, and results of this study are given in Table 1. In each case, **5** was converted to an acylated pyridinium salt in situ by treatment with $EtO_2CCl$. No spirocyclization was observed in dichloromethane (DCM) alone. The presence of a substoichiometric amount of $Ti(O^iPr)_4$ (0.5 equiv), however, almost instantly produced the desired spirodihydropyridine product **6** in excellent (93%) isolated yield (Table 1, entry 2). Lower loadings of $Ti(O^iPr)_4$

(5) (a) Zhou, X.; Kovalev, E. G.; Klug, J. T.; Khodorkovsky, V. *Org. Lett.* **2001**, *3*, 1725. (b) Martín-Cantalejo, Y.; Sáez, B.; Soto, J.; Villa, M. J.; Braña, M. F. *Synthesis* **2003**, 2211. (c) Wagner, R.; Wiedel, B.; Günther, W.; Görls, H.; Anders, E. *Eur. J. Org. Chem.* **1999**, 2383.

**Table 1.** Preliminary Screening of Spirocyclization Reaction Conditions[a]




| entry | solvent | additive[b] | time (min) | % yield **6**[c] |
|---|---|---|---|---|
| 1 | DCM[d] | none | 30 | trace[e] |
| **2** | **DCM** | **$Ti(O^iPr)_4$** | **5** | **93**[f] |
| 3 | DCM | $Ti(O^iPr)_4$[g] | 5 | trace |
| 4 | DCM | $TiCl_4$ | 30 | 0 |
| 5 | DCM | $SnCl_4$ | 30 | trace |
| 6 | DCM | $InCl_3$ | 30 | trace |
| 7 | DCM | $B(OMe)_3$ | 30 | trace |
| 8 | DCM | $Mg(ClO_4)_2$ | 30 | 0 |
| 9 | DCM | $Pd(OAc)_2$ | 30 | 0 |
| 10 | DCM | $MgBr_2$ | 30 | trace |
| 11 | THF | $Ti(O^iPr)_4$ | 30 | trace |
| 12 | DMF | $Ti(O^iPr)_4$ | 30 | 0 |
| 13 | MeCN | $Ti(O^iPr)_4$ | 5 | 79 |
| 14 | PhMe | $Ti(O^iPr)_4$ | 5 | 77 |

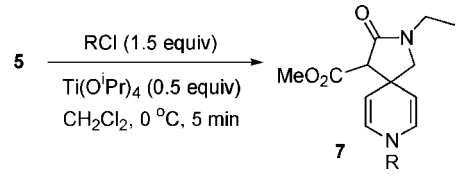
[a] Reactions performed on ~0.5 mmol scale. [b] 0.5 equiv used unless otherwise indicated. [c] Isolated yield. [d] Dichloromethane. [e] Detected by TLC. [f] Optimized yield on ~10 mmol scale. [g] 0.15 equiv used.

were not as effective in promoting the cyclization (Table 1, entry 3), nor were other Lewis acid additives (Table 1, entries 4−10). Besides DCM, several other solvents were screened as well. Reactions performed in THF or DMF were not successful, but spirocyclization was found to occur in MeCN and toluene. Although the mechanistic details of this transformation have not been determined, we speculate that $Ti(O^iPr)_4$ promotes enolization of the $\beta$-dicarbonyl side chain, thereby facilitating nucleophilic addition to the activated pyridinium ring. It is unclear why $Ti(O^iPr)_4$ is the only Lewis acid among those screened that facilitates the reaction.[6] The high-yielding conversion of **5** to **6** shown in entry 2 of Table 1 was used as the basis for a preliminary examination of the scope and limitations of this reaction.

To examine the effect of pyridine acylating agent, substrate **5** was exposed to the reaction conditions indicated in entry 2 of Table 1 except that different electrophiles were used in place of $EtO_2CCl$. As shown in Table 2, alkyl and aryl chloroformates were all reasonably effective in activating the pyridine ring toward nucleophilic addition (Table 2, entries 1−3), and **7a−c** were isolated in good yields. Acetyl chloride and phenylsulfonyl chloride also gave the reaction, albeit with significantly decreased efficiency. Attempted pyridine activation using triflic anhydride, however, produced only an intractable reaction mixture. Likewise, spirocyclization in the presence of methyl iodide also failed.

(6) Formation of $\beta$-dicarbonyl−Ti adducts presumably results in controlled release of isopropoxide, and this may be an important feature of the reaction. Notably, $Ti(O^iPr)_4$ is the only Lewis acid examined that possesses basic counterions. The presence of isopropoxide also resulted in contamination of **6** with trace amounts of the corresponding isopropyl ester **9a**.

**Table 2.** Screening of Pyridine Activating Agents

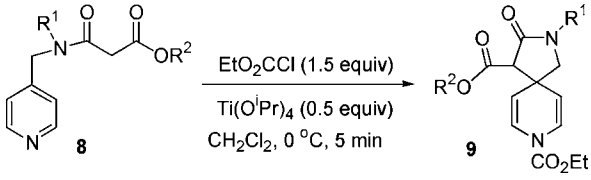



| entry | R | product | % yield[a] |
|---|---|---|---|
| 1 | $^i$PrO$_2$C | **7a** | 80 |
| 2 | BnO$_2$C | **7b** | 86 |
| 3 | PhO$_2$C | **7c** | 66 |
| 4 | CH$_3$C(O) | **7d** | 20 |
| 5 | PhSO$_2$ | **7e** | 13 |
| 6 | CF$_3$SO$_2$[b] | | 0 |
| 7 | Me[c] | | 0 |

[a] Isolated yield. [b] Tf$_2$O was used. [c] MeI was used.

Next, the scope of the cyclization under optimal reaction conditions was examined using several different 4-(aminomethyl)pyridine derivatives (Table 3). As seen, the identity

**Table 3.** Spirocyclization of 4-(Aminomethyl)pyridine Derivatives



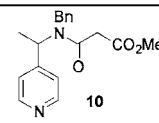
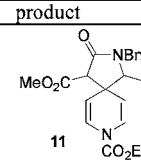
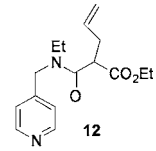
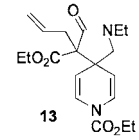
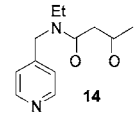
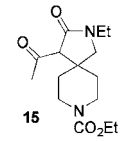
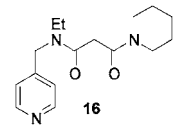
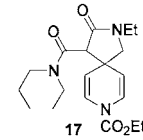
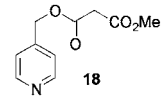
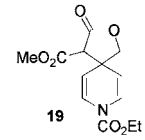
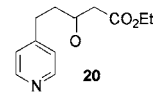
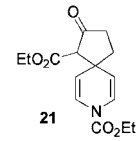
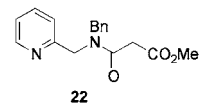
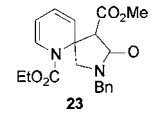

| entry | substrate | $R^1$ | $R^2$ | product | % yield[a] |
|---|---|---|---|---|---|
| 1 | **8a** | Et | $^i$Pr | **9a** | 79 |
| 2 | **8b** | Et | $^t$Bu | **9b** | 68 |
| 3 | **8c** | Et | Bn | **9c** | 73 |
| 4 | **8d** | Et | allyl | **9d** | 71 |
| 5 | **8e** | Bn | Me | **9e** | 69 |
| 6 | **8f** | allyl | Me | **9f** | 90 |
| 7 | **8g** | PMB | Me | **9g** | 90 |

[a] Isolated yield.

of the ester group could be varied without significantly affecting reaction efficiency (Table 3, entries 1−4). Additionally, substrates in which the amide nitrogen was protected with easily removable substituents (Bn, allyl, PMB) could also be converted to the corresponding spirodihydropyridines in good yields.

Additional permutations in the nature of the spirocyclization substrate were next examined. The compatibility of a benzylic substituent with the cyclization reaction was successfully demonstrated through conversion of **10** to dihydropyridine **11** (Table 4, entry 1). No reaction was observed, however, in a substrate bearing an activated methine group in place of an activated methylene (Table 4, entry 2). Acetoacetylated (aminomethyl)pyridine **14** gave the reaction,

**Table 4.** Initial Scope of Pyridine Spirocyclization[a]

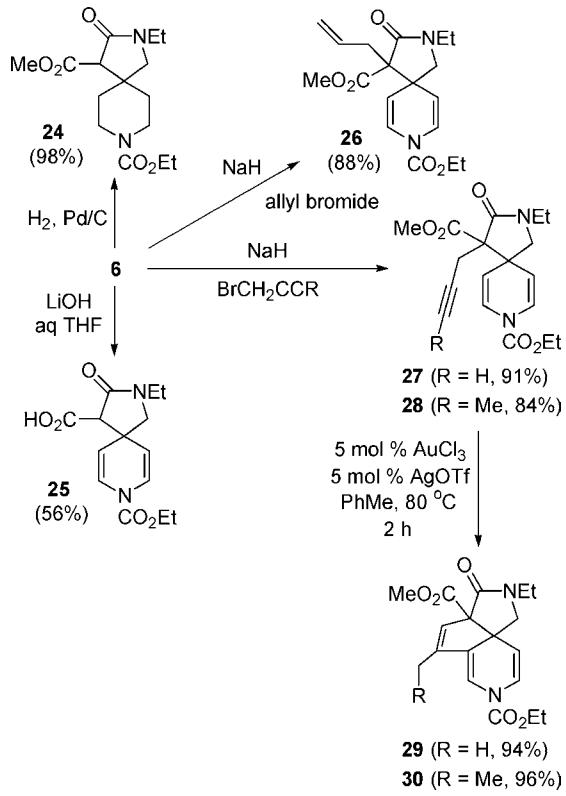
| entry | substrate | product | % yield[b] |
|---|---|---|---|
| 1 |  **10** |  **11** | 81[c] |
| 2 |  **12** |  **13** | n.p.[d] |
| 3 |  **14** |  **15** | 33 |
| 4 |  **16** |  **17** | 68 |
| 5 |  **18** |  **19** | 7 |
| 6 |  **20** |  **21** | n.p. |
| 7 |  **22** |  **23** | n.p. |

[a] Reactions performed according to the conditions given in Table 3 using ~0.5 mmol of the indicated substrate. [b] Isolated yield. [c] Obtained as ~2.7:1 mixture of diastereomers. [d] No product was obtained.

but **15** was isolated in only modest yield. In contrast, the $\beta$-diamide **16** afforded cyclized product in a yield comparable to those obtained using ester-amide analogues (Table 4, entry 4). Attachment of the $\beta$-dicarbonyl unit to the pyridine ring through an ester or ketone linkage, however, had a negative impact upon the reaction, and no cycloadduct could be isolated from reactions of the conformationally flexible substrate **20**. Attempts to prepare spiro-1,2-dihydropyridines from 2-substituted pyridine precursors (e.g., **22**) also failed, perhaps due to unfavorable steric interactions between the pyridine side chain and the carbamate moiety.

The Ti(O$^i$Pr)$_4$-mediated cyclizations described above offer an experimentally simple and mild method for the rapid construction of structurally varied spiro-1,4-dihydropyridines, particularly those featuring a diaza [4.5]decane framework. The ability to further functionalize these heterocyclic building blocks has been briefly examined using **6** as a representative substrate (Scheme 2). Not surprisingly, simple heterogeneous hydrogenation of **6** proceeded efficiently to afford the spiropiperidine analogue **24** in excellent yield. Additionally,

**Scheme 2**




saponification of the pendant ester substituent present on the lactam ring proceeded smoothly to give the corresponding acid **25**. Alkylation of the lactam ring can also be easily accomplished as illustrated in the synthesis of allylated derivative **26**. Notably, this alkylation protocol circumvents an apparent limitation of the spirocyclization procedure involving the use of substituted $\beta$-dicarbonyl substrates (see Table 4, entry 2). Alkylation of **6** with propargyl and butynyl bromide was achieved as well to afford dihydropyridines **27** and **28**. These materials were further elaborated by engaging the 1,6-enyne moieties in Au(III)-catalyzed cycloisomerizations, and tricyclic products **29** and **30** were isolated in excellent yield.[7−9] These last transformations demonstrate the ability to efficiently access structurally complex heterocyclic frameworks from simple pyridine derivatives in only three synthetic operations and in ∼80% overall yield.

In summary, a new and simple method for the preparation of spiro-1,4-dihydropyridine derivatives has been developed. These dihydropyridines can serve as versatile synthetic building blocks in organic and bio-organic chemistry as demonstrated by the preparation of spiropiperidines as well as structurally more complex heterocyclic ring systems. Current work is focused on gaining a better understanding of the unique role played by $Ti(O^iPr)_4$ in the spirocyclization event, further expanding the scope of this transformation, and developing asymmetric variants.

**Acknowledgment.** We thank the Roy J. Carver Charitable Trust for generous financial support (Grant No. 09-3279).

**Supporting Information Available:** Experimental procedures, NMR spectra, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) For a review of Au-catalyzed cycloisomerization, see: Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326.

(8) There are only a few reports describing the participation of enamides in metal-catalyzed cycloisomerizations: (a) Kozak, J. A.; Dodd, J. M.; Harrison, T. J.; Jardine, K. J.; Patrick, B. O.; Dake, G. R. *J. Org. Chem.* **2009**, *74*, 6929, and references cited therein. (b) Harrison, T. J.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2007**, *9*, 367. (c) Harrison, T. J.; Dake, G. R. *Org. Lett.* **2004**, *6*, 5023.

(9) Cycloisomerization likely proceeds via activation of the alkyne by the Au(III) catalyst followed in sequence by nucleophilic addition of the enamide, elimination of $H^+$, proto-demetalation, and isomerization of the initially formed exocyclic olefin. Control experiments established the need for both $AuCl_3$ and AgOTf for efficient cycloisomerization. No reaction occurred in the presence of TfOH alone.