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Electrophilic Activation of Lactams with Tf_2O and Pyridine: Expedient Synthesis of (±)-Tetraponerine T4

André B. Charette,* Simon Mathieu, and Jonathan Martel

Département de Chimie, Université de Montréal, P.O. Box 6128, Station Downtown, Montréal, Québec, Canada, H3C 3J7

andre.charette@umontreal.ca

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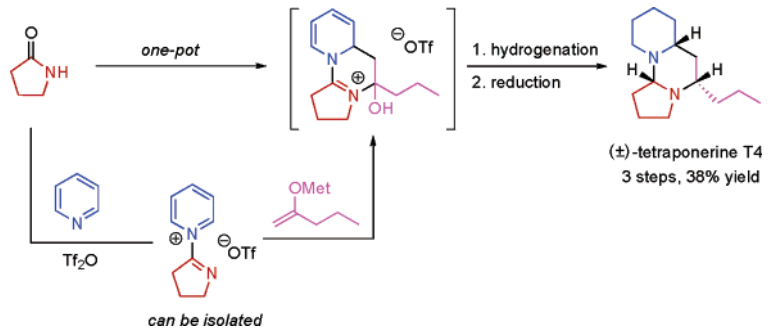
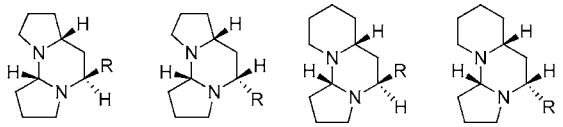
ABSTRACT



The electrophilic activation of lactams with triflic anhydride in the presence of pyridine was investigated by NMR. It was found that 2-pyrrolidone led to the clean formation of the corresponding pyridinium imidate in 89% isolated yield. The subsequent nucleophilic addition of organometallic reagents led to 2-substituted dihydropyridines. A synthesis of (±)-tetraponerine T4 with three simple building blocks was accomplished in 3 steps (38% yield).

Tetraponerines are natural alkaloids isolated from the venom of the New Guinean ant *Tetraponera sp.* (Scheme 1).[1] Since their isolation, several diastereoselective[2] and enantioselective[3] syntheses have been reported. Herein is presented a highly expedient synthesis of (±)-tetraponerine T4 that is based on the rapid and efficient assembly of three components.

Scheme 1. Tetraponerines **T1**−**T8**



T1 R = C_3H_7 **T2** R = C_3H_7 **T3** R = C_3H_7 **T4** R = C_3H_7
T5 R = C_5H_{11} **T6** R = C_5H_{11} **T7** R = C_5H_{11} **T8** R = C_5H_{11}

Our retrosynthetic strategy is depicted in Scheme 2. Tetraponerine T4 could be derived from the piperidine intermediate **1** after the cyclization of the amidine moiety

(1) (a) Merlin, P.; Braekman, J. C.; Daloze, D.; Pasteels, J. M. *J. Chem. Ecol.* **1988**, *14*, 517−527. (b) Braekman, J. C.; Daloze, D.; Pasteels, J. M.; Vanhecke, P.; Declercq, J. P.; Sinnwell, V.; Franke, W. Z. *Naturforsch.* **1987**, *42c*, 627−630.

(2) (a) Kim, J. T.; Butt, J.; Gevorgyan, V. *J. Org. Chem.* **2004**, *69*, 5638−5645. (b) Kim, J. T.; Gevorgyan, V. *Org. Lett.* **2002**, *4*, 4697−4699. (c) Takahata, H.; Kubota, M.; Ikota, N. *J. Org. Chem.* **1999**, *64*, 8594−8501. (d) Barluenga, J.; Tomás, M.; Kouznetsov, V.; Rubio, E. *J. Org. Chem.* **1994**, *59*, 9, 3699−3700. (e) Merlin, P.; Braekman, J. C.; Daloze, D. *Tetrahedron* **1991**, *47*, 3805−3816. (f) Jones, T. H. *Tetrahedron Lett.* **1990**, *31*, 4543−4544. (g) Jones, T. H. *Tetrahedron Lett.* **1990**, *31*, 1538−1541. (h) Merlin, P.; Braekman, J. C.; Daloze, D. *Tetrahedron Lett.* **1988**, *29*, 3805−3816.

(3) (a) Stragies, R.; Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584−9591. (b) Plehiers, M.; Heilporn, S.; Ekelmans, D.; Leclercq, S.; Sangermano, M.; Braekman, J. C.; Daloze, D. *Can. J. Chem.* **2000**, *78*, 1030−1034. (c) Yue, C.; Gauthier, I.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1996**, *61*, 4949−4954. (d) Devijver, C.; Macours, P.; Braekman, J. C.; Daloze, D.; Pasteels, J. M. *Tetrahedron* **1995**, *51*, 10913−10922. (e) Macours, P.; Braekman, J. C.; Daloze, D. *Tetrahedron* **1995**, *51*, 1415−1428. (f) Yue, C. Y.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1990**, *55*, 1140−1141.

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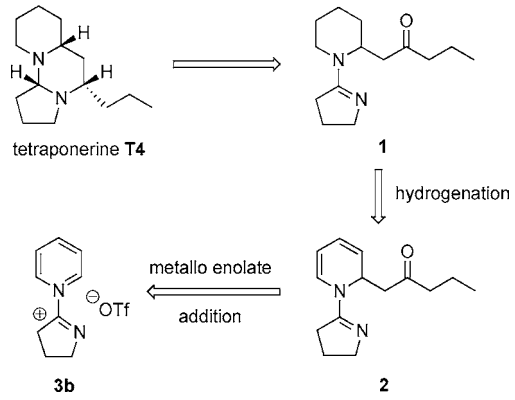
Scheme 2



onto the carbonyl group and reduction. This piperidine would come from pyridinium salt **3b** through a chemoselective hydrogenation of the double bonds, and regioselective addition of a suitable nucleophile at the 2-position of the pyridinium ring. This approach relies on our ability to add nucleophiles to pyridinium salts such as **3b** that are prepared from lactams.

Pioneering work, namely by the group of Comins and others, on metallo enolate addition on both achiral[4] and chiral[5] 1-acylpyridinium salts has been reported, affording the corresponding dihydropyridines (or dihydropyridones).

Over the past few years, we have shown that the activation of amides using triflic anhydride in the presence of pyridine generates pyridinium salts **A**−**C**.[6,7,8] A variety of functional groups are then accessible upon quenching with the appropriate nucleophile (Figure 1).[9]

Due to the competitive *N*-triflation pathway occurring in the activation of lactams with triflic anhydride,[10] only a few

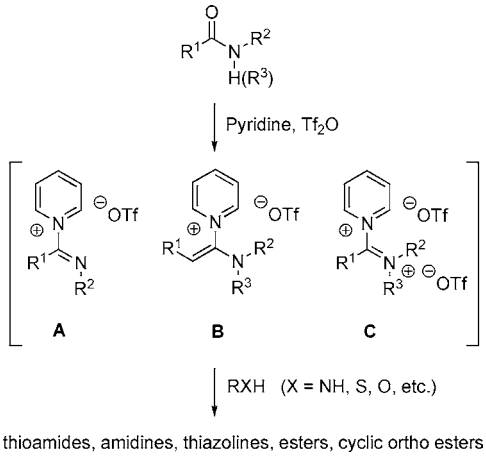
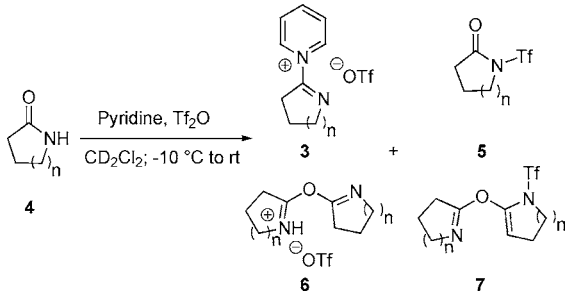


Figure 1. Pyridinium salt formation from amides, Tf_2O, and pyridine: access to various functional groups.

examples of formation of endocyclic iminium or imino triflates (*O*-triflation) have been reported with lactams.[9a,11] Thus, our interest in natural product synthesis led us to submit several lactams to the activation protocol to establish which ones cleanly generated the endocyclic pyridinium imidate **3**.

The activation of four- to seven-membered-ring lactams with triflic anhydride/pyridine was monitored by ^1H and ^{19}F NMR, and the product distribution is shown in Table 1.

Table 1. Activation of Four- to Seven-Membered-Ring Lactams with Tf_2O



entry	*n*	**3**:**5**:**6**:**7**[a]
1	0 (**4a**)	messy
2	1 (**4b**)	>95:<5:0:0
3	2 (**4c**)	45:55:0:0
4	3 (**4d**)	53:0:29:18

[a] Ratio determined by ^1H NMR.

Not surprisingly, the treatment of the β-lactam **4a** led to a mixture of unidentifiable products containing olefinic protons among others. Attempts to isolate either the starting material back upon quenching with water or a dihydropyridine upon Grignard addition failed.[12] Conversely, the activation of the five- or six-membered-ring lactam was very clean, leading to the desired pyridinium salts that contained

(4) (a) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 2219−2222. (b) Courtois, G.; Al-arnaout, A.; Miginiac, L. *Tetrahedron Lett.* **1985**, *26*, 1027−1030. (c) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1984**, *25*, 3297−3300. See also for addition of silyl enol ethers: (d) Wada, M.; Nishihara, Y.; Akiba, K. *Tetrahedron Lett.* **1985**, *26*, 3267−3270. (e) Akiba, K.; Iseki, Y.; Wada, M. *Tetrahedron Lett.* **1982**, *23*, 429−432.

(5) (a) Kuethe, J. T.; Comins, D. L. *J. Org. Chem.* **2004**, *69*, 5219−5231. (b) Kuethe, J. T.; Comins, D. L. *Org. Lett.* **2000**, *2*, 855−857. (c) Comins, D. L.; Kuethe, J. T.; Hong, H.; Lakner, F. J.; Concolino, T. E.; Rheingold, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 2651−2652. (d) Comins, D. L.; Hong, H. *J. Am. Chem. Soc.* **1993**, *115*, 8851−8852. (e) Comins, D. L.; Hong, H. *J. Org. Chem.* **1993**, *58*, 5035−5036.

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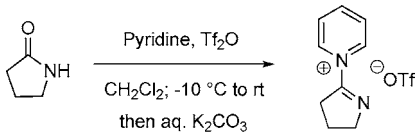
(9) (a) Thioamides, see: Charette, A. B.; Grenon, M. *J. Org. Chem.* **2003**, *68*, 5792−5794. (b) Charette, A. B.; Chua, P. *Tetrahedron Lett.* **1998**, *39*, 245−248. (c) Amidines, see: Charette, A. B.; Grenon, M. *Tetrahedron Lett.* **2000**, *41*, 1677−1680. (d) Thiazolines, see: Charette, A. B.; Chua, P. *J. Org. Chem.* **1998**, *63*, 908−909. (e) Esters, see: Charette, A. B.; Chua, P. *Synlett* **1998**, 163−165. (f) Cyclic ortho esters, see: Charette, A. B.; Chua, P. *Tetrahedron Lett.* **1997**, *38*, 8499−8502.

(10) (a) Mans, D. M.; Pearson, W. H. *J. Org. Chem.* **2004**, *69*, 6419−6426. (b) Chacun-Lefèvre, L.; Joseph, B.; Mérour, J.-Y. *Tetrahedron* **2000**, *56*, 4491−4499. (c) Nagai, S.; Kato, N.; Ueda, T.; Oda, N.; Sakakibara, J. *Heterocycles* **1986**, *24*, 907−912. (d) Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, *46*, 4607−4610.

various amounts of the *N*-triflated product (3% and 55%, respectively) (Table 1, entries 2 and 3). Finally, the seven-membered-ring lactam **4d** led to a mixture of **3d**, **6d**, and **7d** under the same reaction protocol, indicating that the *O*-triflation was the major reaction pathway (Table 1, entry 4). The use of excess reagents or the reverse addition protocol could minimize the formation of **6d** and **7d**.

The cyclic pyridinium salts of type **A**−**C** are typically readily hydrolyzed back to the corresponding amides upon quenching with aqueous solutions. On the contrary, the pyridinium salts **3b**−**d** derived from lactams were surprisingly robust to aqueous workup (neutral or mildly basic conditions). Indeed, pyridinium salt **3b** was isolated in 89% yield after flash chromatography on silica gel when the reaction was directly quenched with a small quantity of aqueous K_2CO_3 followed by drying with Na_2SO_4 (Scheme 3).[13]

Scheme 3



An X-ray crystal structure of **3b** was obtained (Figure 2).[14,15]

Recently, we have reported the highly regio- and diastereoselective addition of organometallic reagents to pyridinium salt **A** derived from a valinol-derived amide to form 2-substituted 1,2-dihydropyridines.[16] This work was further extended to the synthesis of 2,3-disubstituted piperidines[17] and 2-substituted 3-amino-1,2,3,6-tetrahydropyridines,[18] as well as 2,6-disubstituted-3-piperidinols.[19]

With pyridinium salt **3b** in hand, several organometallic nucleophiles were then added, to afford 1,2-dihydropyridines in good to excellent yields (Table 2).

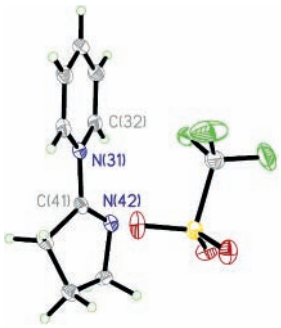


Figure 2. ORTEP diagram of pyridinium salt **3b**. Selected bond lengths (Å) and angles (deg): C(32)−N(31)−C(41), 118.3(4); N(31)−C(41)−N(42), 118.8(4); N(31)−C(41), 1.452(7).

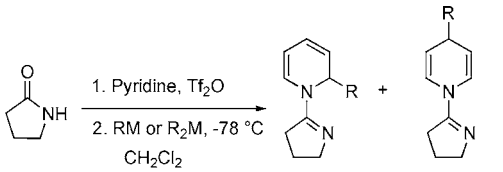
The regioselectivity was found to be excellent in almost all the cases. The presence of the 1,4-adduct could only be observed for the addition of allylmagnesium bromide (Table 2, entry 7). Moreover, the use of Me_2Zn led to the clean addition product **8a** in 67% yield (Table 2, entry 2).

Conversely, the addition of a metallo enolate to the pyridinium salt derived from 2-pyrrolidone was not straightforward (Table 3).

Typically, a mixture of the 1,2-addition product **10**[20] and the 1,4-addition product **11** was formed in a combined yield of 64−81%. Interestingly, none of the ketone **2** could be isolated. Even though our optimal yield was 42% for the 1,2-dihydropyridine **10** (Table 3, entry 4), we have accessed in one step a late intermediate of tetraponerine T4 entirely from commercial reagents.

With the late intermediate (**10**) in hand, the two double bonds were hydrogenated, leading to the corresponding piperidine.[21] The latter was then directly reduced stereose-

Table 2. Nucleophilic Addition to Pyridinium Salt Derived from **4b**



entry	RM or R_2M	**8**,**9**[a]	yield **8** (%)[b]
1	MeMgBr	> 95:5	88 (**8a**)
2	Me_2Zn[c]	> 95:5	67 (**8a**)
3	EtMgBr	> 95:5	89 (**8b**)
4	Et_2Zn[d]	> 95:5	86 (**8b**)
5	PhMgBr	> 95:5	89 (**8c**)
6		> 95:5	88 (**8d**)
7		85:15	76 (**8e**)[e]

[a] Ratio determined by ^1H NMR. [b] Isolated yield of **8**. [c] Me_2Zn added at room temperature. [d] Et_2Zn added at −20 °C. [e] Combined yield of dihydropyridines **8e** and **9e**.

(11) (a) Kuhnert, N.; Clemens, I.; Walsh, R. *Org. Biomol. Chem.* **2005**, *3*, 1694−1701. (b) Rashatasakhon, P.; Padwa, A. *Org. Lett.* **2003**, *5*, 189−191. (c) Padwa, A.; Crawford, K. R.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* **2003**, *68*, 2609−2617. (d) Vonhoff, S.; Vasella, A. *Synth. Commun.* **1999**, *29*, 551−560.

(12) See Supporting Information for detailed protocols and NMR monitoring of each reaction.

(13) Reaction of isolated **3b** with EtMgBr in our standard conditions (see Table 2) gave dihydropyridine **8b** in 91% yield.

(14) Initially obtained as a powder, **3b** was recrystallized from acetone/Et_2O to provide single crystals suitable for X-ray analysis.

(15) For examples of related *N*-acylpyridinium salt isolation, see: (a) Wagner, R.; Wiebel, B.; Günther, W.; Görls, H.; Anders, E. *Eur. J. Org. Chem.* **1999**, 2383−2390 and references therein. (b) Singh, P.; Comins, D. L.; Joseph, S. P. *Acta Crystallogr.* **1994**, *C50*, 25−27. (c) King, J. A.; Bryant, G. L. *J. Org. Chem.* **1992**, *57*, 5136−5139. (d) Bryant, G. L.; King, J. A. *Acta Crystallogr.* **1992**, *C48*, 2036−2039.

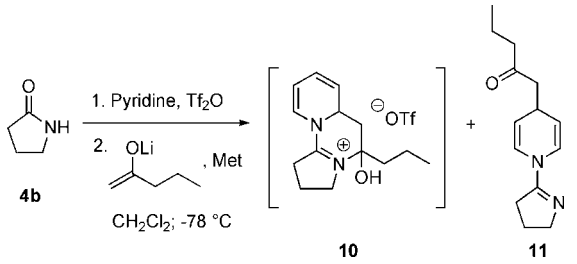
(16) Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829−11830.

(17) Lemire, A.; Grenon, M.; Pourashraf, M.; Charette, A. B. *Org. Lett.* **2004**, *6*, 3517−3520.

(18) Lemire, A.; Beaudoin, D.; Grenon, M.; Charette, A. B. *J. Org. Chem.* **2005**, *70*, 2368−2371.

(19) Lemire, A.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2747−2750.

Table 3. Metallo Enolate Addition to Pyridinium Salt Derived from **4b**



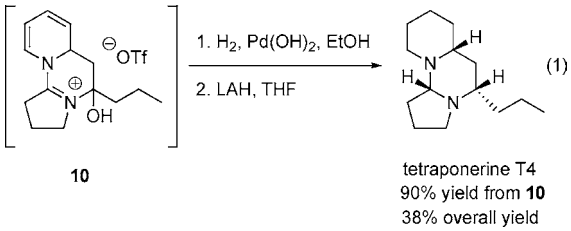
entry	metal salt (Met)[a]	yield **10** (%)[b]	yield **11** (%)[b,c]
1	$MgBr_2 \cdot OEt_2$	35	35
2	$ZnCl_2$	31	33
3	$TiCl(OiPr)_3$	24	40
4	none	42	39

[a] The metal salt was added to the lithium enolate in THF/Et_2O and was stirred for 1 h at −78 °C prior to addition to pyridinium salt **3b**. [b] Yield obtained with trichloroethylene as internal standard. [c] Combined yield of **11** and another unidentified addition adduct.

lectively with LAH, based on a similar strategy used by Gevorgyan et al. to synthesize (±)-tetraponerine T6.[2a,b] Thus, after this two-step, one-purification process (eq 1), (±)-tetraponerine T4 was obtained as a single diastereomer in 90% yield from dihydropyridine **10**, and an overall yield of 38% in three steps and two purifications. This constitutes the shortest synthesis of (±)-tetraponerine T4 reported so far.

(20) **10** was obtained as a mixture of two diastereomers since two distinct patterns of signals were observed by ^{1}H NMR. Our structural assignment of **10** is further supported by the presence of two quaternary centers at 82 (major diastereomer) and 85 ppm (minor diastereomer) by ^{13}C NMR.

(21) This intermediate, as a mixture of diastereomers, was shown to still be an amidinium salt, due to the presence of a CF_3 signal by ^{13}C and ^{19}F NMR.



In conclusion, we have shown that the electrophilic activation of five- and six-membered-ring lactams with triflic anhydride in the presence of pyridine gives the corresponding pyridinium salts, albeit with side-products in some cases. In particular, 2-pyrrolidone gave a very clean formation of the corresponding pyridinium salt, isolated in 89% yield, and was surprisingly stable to aqueous media. The structure of this salt was further confirmed by an X-ray crystal structure. Upon addition of organometallic nucleophiles, this pyridinium salt afforded 2-substituted dihydropyridines in good to excellent yields. Finally, it was applied to the concise (3 steps, 38% overall yield) synthesis of (±)-tetraponerine T4.

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Supporting Information Available: General information, experimental procedures, and characterization data for all new compounds as well as X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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