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One-Pot Formation of Piperidine- and Pyrrolidine-Substituted Pyridinium Salts via Addition of 5-Alkylaminopenta-2,4-dienals to *N*-Acyliminium Ions: Application to the Synthesis of (±)-Nicotine and Analogs

Sabrina Peixoto, Tuan Minh Nguyen, David Crich, Bernard Delpech,* and Christian Marazano†

Centre de Recherche de Gif, Institut de Chimie des Substances Naturelles, CNRS, Avenue de la Terrasse, 91198 Gif-sur-Yvette Cedex, France

bernard.delpech@icsn.cnrs-gif.fr

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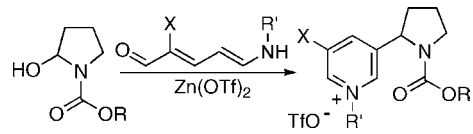
ABSTRACT



Addition of 5-alkylaminopenta-2,4-dienals onto *N*-acyliminium ions, generated in situ from α-hydroxycarbamates derived from pyrrolidine or piperidine, in the presence of zinc triflate, followed by dehydrative cyclization, allowed the formation of pyridinium salts substituted at their 3-position by a five- or six-membered nitrogen heterocycle. Subsequent N-dealkylation of the pyridinium moiety and deprotection of the secondary amine or reduction of the carbamate function led to (±)-nicotine and analogs.

Continuing our long-standing interest in the chemistry of the 5-alkylaminopenta-2,4-dienals,[1−3] we have conducted an investigation into a previously unexplored facet of their reactivity, that of reaction with *N*-acyliminium ions, and report here on our results. In particular, we disclose an unprecedented mild process which leads to a rapid construction of pyridinium salts bound at C-3 to the 2-position of a nitrogen heterocycle, and its application to syntheses of (±)-nicotine and analogs.

It has been shown recently that it was possible to achieve the nucleophilic addition of 5-alkylaminopenta-2,4-dienals onto 2,3-dihydropyridinium ions, generated in situ from their protected aminonitrile counterparts with zinc triflate.[2c,3b] This prompted us to examine the nucleophilic properties of aminopentadienals **2** toward the more electrophilic *N*-acyliminium ions **3**,[4] the formation of which often involves the treatment of α-hydroxy-amides or -carbamates **1** with a Lewis acid. Thus, it was anticipated that the adduct **4** resulting from the attack of the aminopentadienal, for which C-4 is more nucleophilic than C-2,[2b] might further cyclize

† Deceased November 12, 2008.

(1) For a review on aminopentadienals, see: (a) Becher, J. *Synthesis* **1980**, 589–612. For their preparation, see: (b) Nguyen, T. M.; Peixoto, S.; Ouairy, C.; Nguyen, T. D.; Bénéchie, M.; Marazano, C.; Michel, P. *Synthesis* **2010**, 103–109. For recent works with aminopentadienals, see: (c) Michels, T. D.; Kier, M. J.; Kearney, A. M.; Vanderwal, C. D. *Org. Lett.* **2010**, *12*, 3093–3095, and references therein.

(2) (a) Kaiser, A.; Billot, X.; Gateau-Olesker, A.; Marazano, C.; Das, B. C. *J. Am. Chem. Soc.* **1998**, *120*, 8026–8034. (b) Jakubowicz, K.; Ben Abdeljelil, K.; Herdemann, M.; Martin, M.-T.; Gateau-Olesker, A.; Al Mourabit, A.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1999**, *64*, 7381–7387. (c) Wypych, J.-C.; Nguyen, T. M.; Nuhant, P.; Bénéchie, M.; Marazano, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 5418–5421.

(3) (a) Nuhant, P.; Raikar, S. B.; Wypych, J.-C.; Delpech, B.; Marazano, C. *J. Org. Chem.* **2009**, *74*, 9413–9421. (b) Sinigaglia, I.; Nguyen, T. M.; Wypych, J.-C.; Delpech, B.; Marazano, C. *Eur. J. Chem.* **2010**, *16*, 3594–3597.

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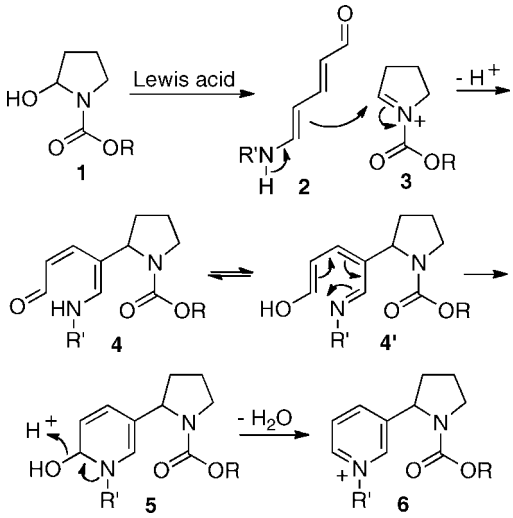
through its tautomeric form **4′** into a pyridinium ion **6** via a dehydrative process (Scheme 1).[5]

Scheme 1. Principle of the Addition-Cyclization Involving a 5-Alkylaminopenta-2,4-dienal **2** and an *N*-Acyliminium Ion **3**

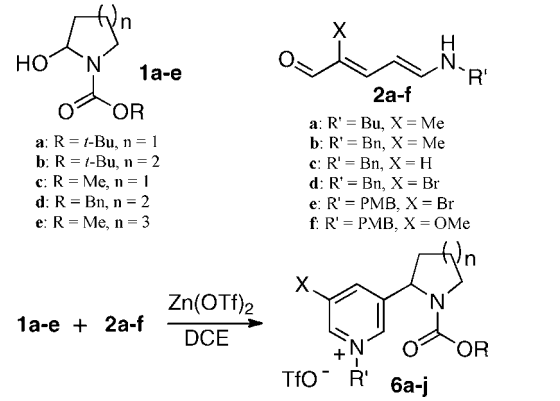


The precursors for the *N*-acyliminium ions were prepared classically through *N*-acylation of the corresponding lactams, followed by reduction with lithium triethylborohydride.[4,6] Aminopentadienals were obtained by treatment of the corresponding glutaconaldehyde potassium salts with a primary amine in the presence of trifluoroacetic acid.[1b]

The choice of the Lewis acid was crucial since it had to promote the *N*-acyliminium ion formation, without inducing prior aminopentadienal dehydrative cyclization to a pyridinium ion.[7] On the basis of precedent,[2c,3b] it was expected that with zinc triflate,[8] this cyclization might occur only after the addition of the nucleophilic species onto the iminium moiety.

In practice, when a solution of hydroxycarbamate **1** and aminopentadienal **2** in 1,2-dichloroethane (DCE) was heated in the presence of 0.5 equiv of $Zn(OTf)_2$,[2c,3b] the pyridinium salt **6** could be isolated with the yields reported in Table 1. This amount of the Lewis acid is sufficient to promote the generation of the intermediate *N*-acyliminium ion and to provide the triflate counterion of the final pyridinium salt. In some cases, TFA was added at the end of the reaction to drive the cyclization to completion.

Table 1. One-Pot Formation of Pyridinium Salts **6** through the Addition of Aminopentadienals **2** onto *N*-Acyliminium Ions Generated from Hydroxycarbamates **1**[a]



entry	R	R′	X	*n*	product	yield
1	*t*-Bu	Bu	Me	1	**6a**	51%
2	*t*-Bu	Bn	Me	1	**6b**	51%
3	*t*-Bu	Bu	Me	2	**6c**	52%
4	Me	Bn	H	1	**6d**	32%[b]
5	Bn	Bn	H	2	**6e**	45%
6	Me	Bn	Br	1	**6f**	77%[c,d]
7	Me	PMB	Br	1	**6g**	86%[d]
8	Bn	Bn	Br	2	**6h**	24%[d]
9	Me	Bn	Br	3	**6i**	82%[d]
10	Me	PMB	OMe	1	**6j**	17%[d]

[a] Conditions: 1.2 equiv of **2** and 0.5 equiv of $Zn(OTf)_2$, DCE, reflux 14 h. [b] 28% of **7** was isolated. [c] At rt, 54% of **6f** and 27% of **4f**[9] were isolated. [d] TFA (1 equiv) was added at rt, after heating, and the mixture stirred for cyclization (**4** to **6**) completion (1 h).

From Table 1, it is clear that the reaction can be conducted starting with five- to seven-membered hydroxycarbamates and that it is more efficient if there is a substituent, such as CH_3 or Br, at the 2-position of the aminopentadienal. The yields are lower when X = H (entries 4 and 5) and, in the pyrrolidine case (entry 4), **7** was isolated as a byproduct. This compound resulted from the addition of the aminopentadienal, first by its C-4 and then by its C-2, onto two *N*-acyliminium ions and this behavior highlights the nucleophilicity of these two carbons.[1a] When X = Me or Br, this process is less favored for steric reasons. Since the C−Br bond can be hydrogenolysed (vide infra), the bromine atom can be considered here as a protective group. With a stronger electron-donating substituent (OMe) at C-2, the electronic perturbation of the push−pull system might be responsible for the lower efficiency of the reaction (entry 10). The use

(4) For reviews, see: (intramolecular reactions) (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367–4416. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856. (cyclizations) (c) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628. (d) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311–2352. (intermolecular additions) (e) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339−368; *Synthesis* **2009**, 513−541.

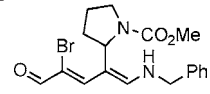
(5) An electrocyclization is a more likely mechanism than an intramolecular nucleophilic addition of the aminopentadienal nitrogen onto its carbonyl functionality; see: (a) Colabroy, K. L.; Begley, T. P. *J. Am. Chem. Soc.* **2005**, *127*, 840–841. This is analogous to the formation of pyridinium salts via the Zincke reaction: (b) Cheng, W.-C.; Kurth, M. J. *Org. Prep. Proc. Int.* **2002**, *34*, 587–608.

(6) Dieter, R. K.; Sharma, R. R. *J. Org. Chem.* **1996**, *61*, 4180–4184.

(7) 5-Alkylaminopenta-2,4-dienals cyclize easily into pyridinium ions in acidic conditions: see ref 1a.

(8) The mild Lewis acid properties of zinc triflate have been exploited for the one-pot generation of *N*-acyliminium ions in the presence of silyl enol ethers: Pilli, R. A.; Robello, L. G. *Synlett* **2005**, 2297–2300.

(9) Structure of compound **4f**.



of (*S*)-α-methylbenzylamine-derived aminopentadienals or of an optically active menthyl carbamate did not induce any significant diastereomeric excess (see Supporting Information).

The procedure depicted in Table 1 was not efficient with aminopentadienal **2d** (R′ = Bn, X = Br), chosen in order to avoid double addition, and the hydroxylactam **8**,[10] derived from *N*-methylsuccinimide (Figure 1), even in the presence

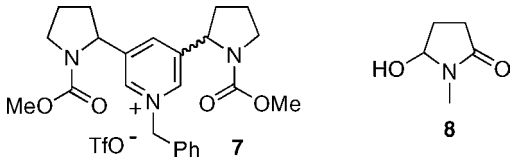
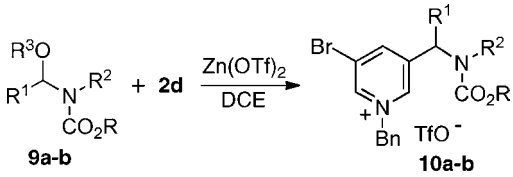


Figure 1. Structures of compounds **7** and **8**.

of 1 equiv of $Zn(OTf)_2$,[11] since the desired product was obtained in 7% yield only. This result could be attributed to the lower stabilization and intrinsically poorer reactivity of the *N*-methylpyrrolidone-derived *N*-acyliminium ion, compared to its carbamate counterparts.[12]

With **2d** as the nucleophilic partner, the pyridinium salts **10** could be obtained, using the open-chain carbamates **9a**[13] and **9b**[14] as *N*-acyliminium ions precursors, through an α-amidoalkylation-type reaction (Scheme 2).

Scheme 2. Formation of Pyridinium Salts **10** via the Addition of Open-Chain *N*-Acyliminium Ions onto Aminopentadienal **2d**[a,b]



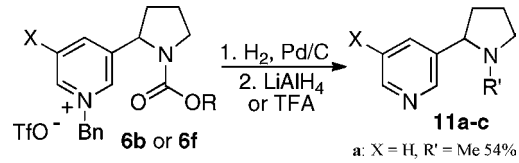
a: R = Bn, R^1 = Me, R^2 = Me, R^3 = H 68%
b: R = Et, R^1 = Ph, R^2 = Bn, R^3 = Et 31%

[a] Same conditions as for Table 1. [b] TFA (1 equiv) was added at rt, after heating, and the mixture stirred for cyclization completion (20 mn).

To illustrate the method, an application to the synthesis of natural pyridine-containing alkaloids, such as nicotine and anabasine, was envisaged. The simplicity of the molecular architecture of these compounds and the important biological profile of nicotine have attracted significant attention from the synthetic chemistry community.[15] Most syntheses in this area rely on the construction of the pyrrolidine or piperidine ring starting from a pyridine derivative. Here, we report a method in which the aromatic heterocycle is built onto a five- or six-membered nitrogen compound.

The *N*-benzylpyridinium salts **6b** and **6f** were subjected to hydrogenolysis of both the $C-N^+$ and C−Br bonds, in the presence of triethylamine for **6f**,[16] to yield the corresponding pyridines. By reduction of the carbamate moiety or acidic treatment, in the case of the Boc derivative, nicotine **11a**, 5-methylnicotine **11b**[17] and 5-methylnornicotine **11c** were obtained (Scheme 3).

Scheme 3. Formation of (±)-Nicotine **11a** and Derivatives from Pyridinium Salts **6b** and **6f**[a]



b: X = Me, R = *t*-Bu
f: X = Br, R = Me

a: X = H, R' = Me 54%
b: X = R' = Me 59%
c: X = Me, R' = H 98%

[a] Significant hydrogenolysis of the benzylic pyrrolidine C−N bond was observed in the case of **6f**.

Since the bromine substituent opens up avenues for the introduction of other functionalities, a method for debenzylation of the pyridinium ion without hydrogenolysis of the C−Br bond was developed. Taking advantage of the leaving group properties of the PMB moiety, due to the stabilization of the *p*-methoxybenzyl cation, a complete transfer of this group onto pyridine was achieved by heating pyridinium salt **6g** in this solvent (Scheme 4).[18] Reduction of the carbamate moiety with $LiAlH_4$ led to 5-bromonicotine **12**,[19] a compound which has previously been converted to the anti-Parkinson's drug SIB-1508Y.[20]

(10) Hubert, J. C.; Wijnberg, J. B.; , P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437–1441.

(11) $Zn(OTf)_2$ (1.2 equiv) was employed in the case of the reactions mentioned in ref 8.

(12) D'Oca, M. G. M.; Moraes, L. A. B.; Pilli, R. A.; Eberlin, M. N. *J. Org. Chem.* **2001**, *66*, 3854–3864.

(13) For the preparation of **6a**, see Supporting Information.

(14) (a) Esch, P. M.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1992**, *48*, 3445–3462. (b) Lumbroso, A.; Chevallier, F.; Beaudet, I.; Quintard, J.-P.; Besson, T.; Le Grognec, E. *Tetrahedron* **2009**, *65*, 9180–9187.

(15) For a recent review on the synthesis of nicotine and its derivatives, see: (a) Wagner, F. F.; Comins, D. L. *Tetrahedron* **2007**, *63*, 8065–8082. For selected syntheses of nicotine and anabasine, see: (b) Felpin, F.-X.; Girard, S.; Vo-Thanh, G.; Robins, R. J.; Villiéras, J.; Lebreton, J. *J. Org. Chem.* **2001**, *66*, 6305–6312. (c) Spangenberg, T.; Breit, B.; Mann, A. *Org. Lett.* **2009**, *11*, 261–264.

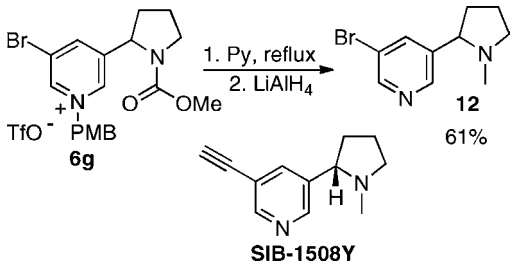
(16) A base is added to trap HBr, released during hydrogenolysis of the C−Br bond, which favors the ring-opening of the *N*-methoxycarbonylpyrrolidine. This could be related to the racemization of nicotine derivatives with chloroformates: Bleicher, L. S.; Cosford, N. D. P. *J. Org. Chem.* **1999**, *64*, 5299–5300.

(17) Racemic compound: (a) Seeman, J. I.; Secor, H. V.; Chavdarian, C. G.; Sanders, E. B.; Bassfield, R. L.; Whidby, J. F. *J. Org. Chem.* **1981**, *46*, 3040–3048. Enantiomerically enriched (*S*)-(−) compound: (b) Chavdarian, C. G.; Sanders, E. B.; Bassfield, R. L. *J. Org. Chem.* **1982**, *47*, 1069–1073. (±)-5-Methylnicotine has the same affinity than nicotine for the α4β2 nicotinic cholinergic receptor: (c) Dukat, M.; Ramunno, A.; Banzi, R.; Damaj, M. I.; Martin, B.; Glennon, R. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4308–4312.

(18) Wanner, M. J.; Koomen, G.-J. *Eur. J. Org. Chem.* **1998**, 889–895.

(19) (a) Castonguay, A.; Van Vunakis, H. *J. Org. Chem.* **1979**, *44*, 4332–4337. (b) Bleicher, L. S.; Cosford, N. D. P.; Herbaut, A.; McCallum, J. S.; McDonald, I. A. *J. Org. Chem.* **1998**, *63*, 1109–1118. For biological activities of (±)-5-bromonicotine, see: (c) Cosford, N. D. P.; Bleicher, L.; Vernier, J.-M.; Chavez-Noriega, L.; Rao, T. S.; Siegel, R. S.; Suto, C.; Washburn, M.; Llyod, G. K.; McDonald, I. A. *Pharm. Acta Helv.* **2000**, *74*, 125–130. (d) Dukat, M.; Damaj, M. I.; Young, R.; Vann, R.; Collins, A. C.; Marks, M. J.; Martin, B. R.; Glennon, R. A. *Eur. J. Pharmacol.* **2002**, *435*, 171–180.

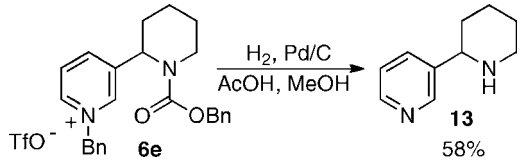
Scheme 4. Synthesis of 5-Bromonicotine **12**[19] from Pyridinium Triflate **6g**[a]



[a] Partial cleavage of the C−Br bond was observed in the reaction with $LiAlH_4$, leading to nicotine **11a** (17%).

The compound **6e** in the six-membered ring series was transformed into (±)-anabasine **13** in one step, taking advantage of the presence of two benzyl groups bound to heteroatoms, through hydrogenolysis in the presence of acetic acid (Scheme 5).[21]

Scheme 5. Formation of (±)-Anabasine **13** by Hydrogenolysis of Pyridinium Triflate **6e**



The methodology reported here displays a new development of the chemistry of aminopentadienals, and also of *N*-acyliminium ions. It may be useful for the synthesis of 1-substituted-1-(pyridyl)methylamines[22] or pyridine-substituted nitrogen heterocycles. This approach supplements the palladium-catalyzed arylation of *N*-Boc-pyrrolidine with 3-bromopyridine.[23] By a judicious choice of the hydroxycarbamate alkyl group and of the aminopentadienal substituents, it is possible to access differents types of pyridinium salts. The use of 2-bromoaminopentadienals is particularly interesting for the further introduction of functionalities on the pyridine ring, for example via metal-catalyzed couplings.[24] Moreover, *N*-acyliminium ions derived from pyroglutamic acid[25] might be used to introduce asymmetry in the formation of pyridyl-substituted prolines.[26]

In conclusion, addition of 5-alkylaminopenta-2,4-dienals, by their nucleophilic C-4 position, onto *N*-acyliminium ions generated in situ from pyrrolidine- or piperidine-derived α-hydroxycarbamates, followed by subsequent dehydrative cyclization, led to substituted pyridinium salts bound by the 3 position to a saturated nitrogen heterocycle. By further *N*-dealkoxycarbonylation and -dealkylation of selected products, (±)-nicotine or (±)-anabasine and analogs were obtained.

Supporting Information Available: Experimental procedures and copies of ^1H and ^{13}C NMR spectra for compounds **6a**−**j**, **7**, **9a**, **10a**−**b**, **11a**−**c**, **12**, **13** and (*S*)-α-methylbenzylamine-derived aminopentadienals. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Cosford, N. D. P.; Bleicher, L.; Herbaut, A.; McCallum, J. S.; Vernier, J.-M.; Dawson, H.; Whitten, J. P.; Adams, P.; Chavez-Noriega, L.; Correa, L. D.; Crona, J. H.; Mahaffy, L. S.; Menzaghi, F.; Rao, T. S.; Reid, R.; Sacaan, A. I.; Santori, E.; Stauderman, K. A.; Whelan, K.; Llyod, G. K.; McDonald, I. A. *J. Med. Chem.* **1996**, *39*, 3235–3237.

(21) Incomplete hydrogenolysis was observed in the absence of an acid.

(22) For a review on the synthesis of these optically active compounds, see: Chelucci, G. *Tetrahedron: Asymmetry* **2005**, *16*, 2353–2383.

(23) (a) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-y. *J. Am. Chem. Soc.* **2006**, *128*, 3538–3539. For a review on direct sp^3 C−H bond activation adjacent to nitrogen in heterocycles, see: (b) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069–1084.

(24) The Stille reaction has been achieved starting from bromopyridinium salts: García-Cuardrado, D.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *Synlett* **2002**, 1904–1906.

(25) (a) Martin, S. F.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299–3300. (b) Vaswani, R. G. *J. Org. Chem.* **2008**, *73*, 1661–1681. For a recent review on pyroglutamic acid, see: (c) Panday, S. K.; Prasad, J.; Dikshit, D. K. *Tetrahedron: Asymmetry* **2009**, *20*, 1581–1632.

(26) (a) Xu, Y.-z.; Choi, J.; Calaza, M. I.; Turner, S.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 4069–4078. (b) van Esseveldt, B. C. J.; Vervoort, P. W. H.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem.* **2005**, *70*, 1791–1795.