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Stereocontrolled synthesis of polysubstituted piperidines from vinylogous Mannich adducts and aldehydes

José M. Aurrecoechea* and Rubén Suero

Departamento de Química Orgánica II, Facultad de Ciencia y Tecnología, Universidad del País Vasco, Apartado 644, 48080 Bilbao, Spain

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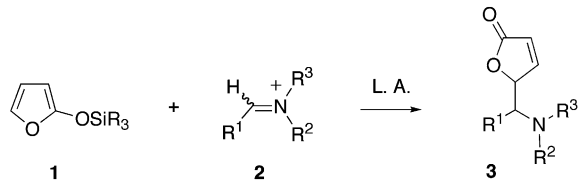
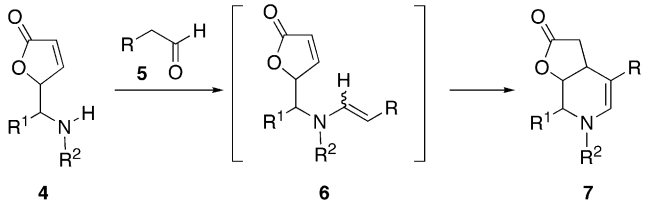
Abstract—Condensation of readily available 5-(aminoalkyl)furan-2-ones, derived from the Mannich-type reaction between 2-silyloxyfurans and acyliminium ions, with an α-unsubstituted aliphatic aldehyde leads to substituted 1,2,3,4-tetrahydropyridines in a process involving an enamine conjugate addition. Reduction of the tetrahydropyridine double bond then affords 3,4,5-tri- or 3,4,5,6-tetra-substituted piperidines stereoselectively.

The vinylogous Mannich reaction[1] between 2-silyloxyfurans **1** and iminium ions **2** (Scheme 1) has found important applications in the synthesis of natural- and related products.[2] Thus, this reaction has been incorporated into a number of reaction schemes where the key C–C bond-formation brought about by the Mannich-type addition of dienolate **1** to **2** is often followed at some stage by manipulation of the conjugated double bond of products **3** that may commonly undergo reduction,[2a,b,g] oxidation[1] or conjugate addition[2c] reactions.

In this letter we disclose that amines **4**, derived from vinylogous Mannich addition products **3** (where R^3 = Boc), afford 1,2,3,4-tetrahydropyridines **7** when condensed with aldehydes **5** under very mild reaction conditions, presumably through the intermediacy of acyclic enamines **6** (Scheme 2). Examples of such an intramolecular enamine endocyclic addition to an α,β-unsaturated carbonyl derivative are found in a key step of the synthesis of Karachin from Berberin,[3] and in some reactions starting from activated enaminone-type substrates.[4] From the strategic point of view, the formation of **7** from **4** and **5** would be related to the previously reported aza-annulation of enamines with acryloyl chloride,[5] as well as to other intramolecular processes involving enamines, such as displacement of a leaving group on primary carbon[6] and addition to an ester carbonyl.[7] However, the actual synthesis of 1,2,3,4-tetrahydropyridines (e.g., **7**) from unsaturated-amine and simple aldehyde precursors has precedent only in one isolated case of spirocyclization employing a phenylacetaldehyde as carbonyl component,[8] and this type of reaction has not been developed synthetically. Tetrahydropyridines **7** are interesting compounds containing a basic bicyclic enamine substructure that can be found in naturally occurring alkaloids of the Corynanthe type.[9] Furthermore, manipulation of the functionality present in **7** would allow the rapid synthesis of structurally



Scheme 1.



Scheme 2.

Keywords: Vinylogous Mannich; Piperidines; Tetrahydropyridines; Enamines.
* Corresponding author. Fax: +34 9460 12748; e-mail: qopaufem@lg.ehu.es

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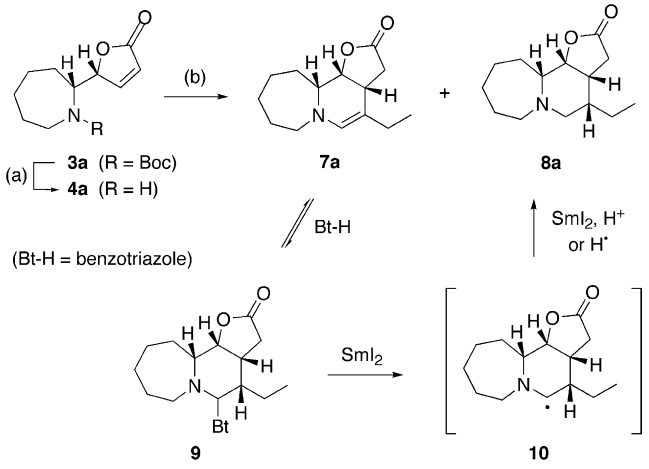
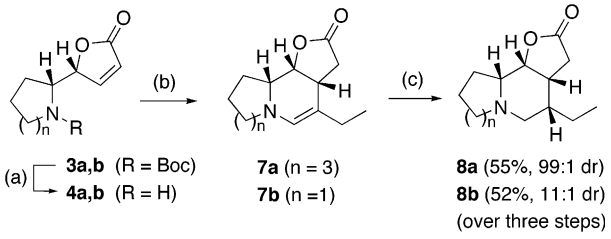


Scheme 3. Reagents and conditions: (a) TFA, CH_2Cl_2, 0 °C → rt. (b) (i) *n*-Butanal, Bt-H, CH_2Cl_2, 4 Å MS, rt. (ii) SmI_2, *t*-BuOH, THF, −78 °C → rt.

diversified polysubstituted piperidine derivatives from readily available amine and aldehyde building blocks.

Our interest in this area arose from the observation that variable amounts of byproducts of type **7** were formed in the SmI_2-promoted cyclization reactions of α-aminoalkyl radicals generated from adducts derived from the condensation of benzotriazole with amines **4** and aldehydes **5**.[10] For example, treatment of amine **4a**[11,12] with *n*-butanal and benzotriazole (Bt-H), followed by SmI_2, afforded the tricyclic compounds **7a** (20%) and **8a** (7%) as the only isolated products (Scheme 3). Upon close inspection of the ^1H NMR spectrum of the crude mixture formed from **4a**, butanal and Bt-H, it was found that at that point some tetrahydropyridine **7a** had already formed. Another product, tentatively assigned as the cyclized benzotriazole-adduct **9**, was also present in the mixture (Scheme 3). This was corroborated by treating isolated **7a** with equimolar Bt-H in $CDCl_3$ whereupon a mixture of **7a** and **9** was produced immediately in a 3:2 ratio that did no change over time. Prolonged treatment with SmI_2 at rt of a similar **7a/9** mixture generated in THF produced the reduction product, piperidine **8a**, presumably through an intermediate α-aminoalkyl radical **10**.[13,14]

It was eventually found that the use of Bt-H was not necessary and that simply stirring **4a** with an equivalent amount of butanal in CH_2Cl_2 at rt in the presence of activated 4 Å MS led to the efficient formation of **7a** as a single diastereoisomer that, after chromatographic purification, was isolated in a 58% yield over two steps starting from the *N*-Boc precursor **3a**[12a,b] (Scheme 4).[†] Catalytic hydrogenation of **7a** led to piperidine **8a** (94% yield) along with a minor diastereoisomer in a 99:1 ratio. The major isomer had an all-*syn* relationship about the four contiguous stereogenic centres, as confirmed by NMR studies.[‡] Furthermore, we found that the scope of this facile tetrahydropyridine synthesis is not restricted to the azepane-based unsaturated amine. For example, pyrrolidine **4b** ($n = 1$),[11,12] obtained from the corresponding *N*-Boc derivative **3b** ($n = 1$),[12a,c] reacted similarly with butanal to afford the rather unstable enamine **7b** (35%) that appeared to decompose partially upon chromatographic purification. That this was the case was indicated by the much more respectable 52% yield (for the combined three steps starting from Boc-protected **3b**) obtained for tricyclic piperidine **8b** (11:1 dr) when the crude enamine **7b** was directly subjected to catalytic hydrogenation (Scheme 4).[†,‡]

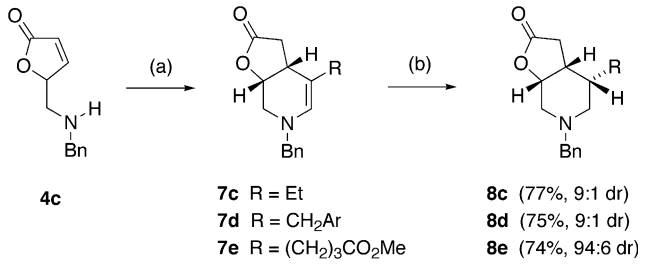


Scheme 4. Reagents and conditions: (a) TFA, CH_2Cl_2, 0 °C → rt (**3a**) or TMSOTf, CH_2Cl_2, −25 → −5 °C (**3b**). (b) *n*-Butanal, CH_2Cl_2, 4 Å MS, rt. (c) H_2 (1 atm), Pd/C, EtOH, rt.

The simpler benzylamine **4c**[15] reacted similarly with aldehydes possessing an unsubstituted α-methylene unit to afford the corresponding bicyclic products **7c–e**. As exemplified in Scheme 5, simple alkyl-, as well as benzyl- and functionalized-alkyl groups are readily incorporated as substituents in the newly created heterocyclic ring. While cyclic products **7c–e** could be chromatographically purified with apparently little loss (e.g., **7e** was obtained in 78% yield after purification), the crude enamines were usually of enough purity for subsequent

[†] The following experimental procedure is representative: Trifluoroacetic acid (5.24 mL, 68.0 mmol) was added dropwise to a solution of **3a** (1.125 g, 4.00 mmol) in CH_2Cl_2 (48 mL) at 0 °C. The cooling bath was removed, the reaction mixture was stirred for 2 h and then it was extracted with sat. K_2CO_3 (50 mL). The aqueous layer was back-extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$) and evaporated to a volume of approximately 50 mL. To this solution was added butyraldehyde (0.35 mL, 4.00 mmol) and 4 Å molecular sieves (8.00 g). The resulting suspension was stirred at rt for 14 h and filtered over Celite. The crude after evaporation was purified by flash chromatography (silica gel saturated with Et_3N, 88:10:2 hexanes/EtOAc/Et_3N) to yield **7a** (547 mg, 58% for two steps). A stirred mixture of **7a** (0.470 g, 2.00 mmol) and 10% Pd/C (0.028 g) in absolute ethanol (24.0 mL) was treated with H_2 (1 atm) for 24 h. The catalyst was filtered off over Celite and the crude after evaporation was purified by flash chromatography (silica gel saturated with Et_3N, 93:5:2 hexanes/EtOAc/Et_3N) to yield **8a** (444 mg, 94%, 99:1 dr).

[‡] The relative stereochemistry of **7a** was deduced as follows. The *syn* relationship between the piperidine 2- and 3-positions followed from the known configuration of the starting material **3a**,[12a] and was confirmed by the NOE observed between the corresponding methine protons. The lactone *cis*-fusion, expected on thermodynamic grounds, was also confirmed by the NOE displayed by the bridgehead protons. For **8a** an additional NOE between the methine proton on the ethyl-bearing carbon and the adjacent bridgehead proton confirmed the all-*syn* stereochemical assignment that was further supported by the shielding of the C-1, C-5 and C-7 ^{13}C NMR resonances (3.4–4.5 ppm) observed in the major isomer of **8a** with respect to the minor one. Compounds **7c–e** and **8c–e** were similarly elucidated, while the stereochemistry of **7b** and **8b** was assigned by analogy with that of **7a** and **8a**.



Scheme 5. Reagents and conditions: (a) RCH_2CHO, CH_2Cl_2, 4 Å MS, rt. (b) H_2 (1 atm), Pd/C, EtOH, rt. Ar = 3,4-dimethoxyphenyl.

chemical transformations. Thus, catalytic hydrogenation yielded *C*-trisubstituted piperidines **8c–e** with high stereoselectivities and very satisfying chemical yields over two steps starting from amine **4c**.[†,‡]

Therefore, it is apparent that with a proper selection of the substituents carried by the amine starting-material and, particularly, of the aldehyde moiety, a flexible synthesis of polysubstituted piperidines with a high degree of structural diversity is at hand. It should be noted that cyclic enamines **7** contain functionality that can be put to uses other than catalytic hydrogenation. For example, enamines related to these have been postulated as intermediates in the preparation of morphan- and indole-derivatives.[16] These ideas, as well as the possibility of performing radical chemistry at the piperidine 2-position through α-aminoalkyl radicals[10b,14] derived from enamines **7**, are actively being pursued in our laboratory.

Acknowledgments

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11. Amines **4a** and **4b** were obtained from acidic deprotection of the known *N*-Boc precursors **3a**[12a,b] and **3b**,[12a,c] respectively. Amines **4a**,**b** decompose under chromatographic purification conditions and also in the absence of solvent. Therefore, they were used in a crude form after partial evaporation of the CH_2Cl_2 extracts from deprotection.
12. Vinylogous Mannich adducts **3a**,**b** were prepared according to: (a) de Oliveira, M. C. F.; Silva-Santos, L.; Pilli, L. A. *Tetrahedron Lett.* **2001**, *42*, 6995–6997, with yields and stereoselectivities in good agreement with the reported data. For other reported preparations of these compounds, see: (b) Suh, Y.-G.; Kim, S.-H.; Jung, J.-K.; Shing, D.-Y. *Tetrahedron Lett.* **2002**, *43*, 3165–3167; (c) Pichon, M.; Figadere, B.; Cave, A. *Tetrahedron Lett.* **1996**, *37*, 7963–7966.
13. Formation of α-aminoalkyl radicals (e.g., **10**) from α-dialkylaminoalkylbenzotriazoles (e.g., **9**) upon treatment with SmI_2 is well documented.[10b,14] It is apparent that radical **10** undergoes either H atom abstraction from the solvent or further reduction to an organosamarium followed by protonation, to afford in either case piperidine **8a**. Whatever the pathway, this was a somewhat surprising outcome since, in the absence of efficient radical traps (e.g., electron-deficient alkenes),[10b,14] **10** would instead be expected to dimerize to afford a vicinal diamine.[14a] It is likely that steric congestion around the radical centre slows down dimerization so that other processes (e.g., H abstraction or reduction) become competitive.
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