Tetrahedron Letters 52 (2011) 6873–6876

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Diastereoselective synthesis of trisubstituted piperidines: a versatile synthon for elaboration of uncommon poly(aza)heterocyclic structures

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ARTICLE INFO

Article history:
Received 12 July 2011
Revised 29 September 2011
Accepted 30 September 2011
Available online 6 October 2011

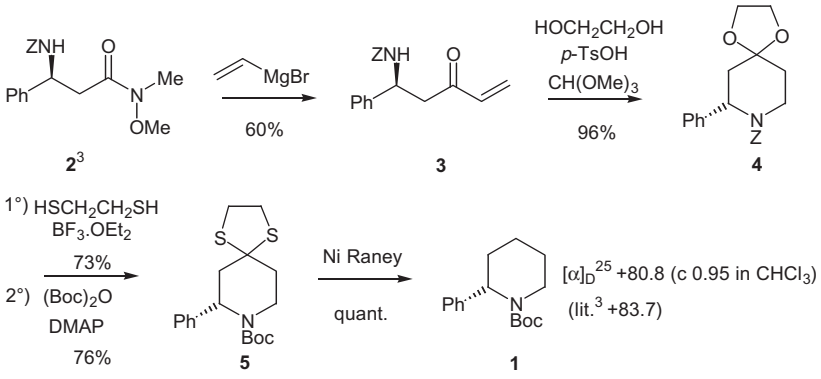
Keywords:
β,β′-Diaminoketals
Diastereoselective synthesis
Octahydro-2*H*-pyrrolo-[3,4-*b*]-pyridine
Intramolecular Mannich reaction
Intramolecular Michael addition

ABSTRACT

Hetero Michael addition on chiral β′-amino-α,β-unsaturated ketone furnished, after some structural modifications, β,β′-diaminoketals. Mannich type reaction of these diamines with an aldehyde led, with a high diastereoselectivity, to trisubstituted piperidines. Starting from a functionalized aldehyde and after subsequent deprotection of the amino group, an intramolecular Michael addition provided octahydro-2*H*-pyrrolo-[3,4-*b*]-pyridine, an uncommon framework found in compounds exhibiting biological activity.

Natural products synthesis, by their structural complexity, is always the source of discovery and innovation of new selective methods which can compete with these provided by the nature. So, there is still a great interest in developing new synthetic pathways which include chemo, regio and stereoselectivity. In this context, we have recently disclosed the diastereoselective synthesis of 2- and 2,6-substituted piperidines using an intramolecular Michael type reaction[1] starting from β′-amino-α,β-unsaturated ketone. The synthesis of *N*-Boc-2-phenylpiperidine **1** is described in Scheme 1 to illustrate this approach.[2]

We wish to describe herein the extension of this methodology to the diastereoselective synthesis of enantiomerically pure 2,3,6-trisubstituted piperidines and their application in the preparation of octahydro-2*H*-pyrrolo-[3,4-*b*]-pyridine, an uncommon framework found in compounds exhibiting biological activity.[4] Initially we planned to take advantage of this newly created Michael



Scheme 1. Diastereoselective synthesis of 2-substituted piperidine.

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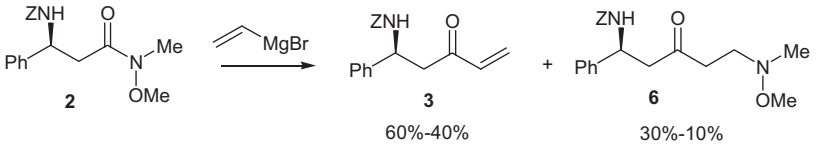
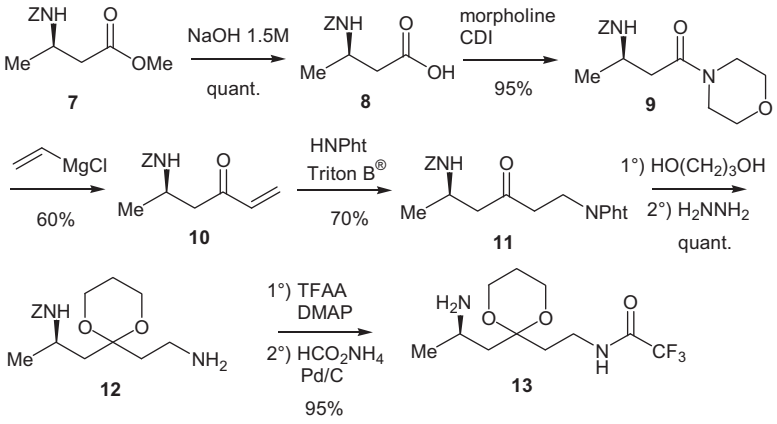
0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.09.148

acceptor **3** to promote the intermolecular introduction of a nucleophile such as various amines. Unfortunately, the use of vinylmagnesium bromide on Weinreb amide **2** provides always a byproduct **6**, in low to moderate yield, resulting from the condensation of *N*,*O*-dimethylhydroxylamine on the new generated double bond[5] (Scheme 2). In consequence, a new pathway to obtain compound of type **3** has to be found.

To develop a new access to β′-amino-α,β-unsaturated ketones, we chose the morpholine route as described in Scheme 3. So, condensation of morpholine with N-protected aminobutanoic acid **8**, available from the saponification of β-aminoester **7**,[6] in the presence of carbonyldiimidazole provided adduct **9** in very good yield. Further alkylation with vinyl Grignard reagent gave as the only reaction product the desired β′-amino-α,β-unsaturated ketone **10**



Scheme 2. Condensation of vinylmagnesium bromide on Weinreb amide.



Scheme 3. Morpholine route to access β,β′-diaminoketal **13**.

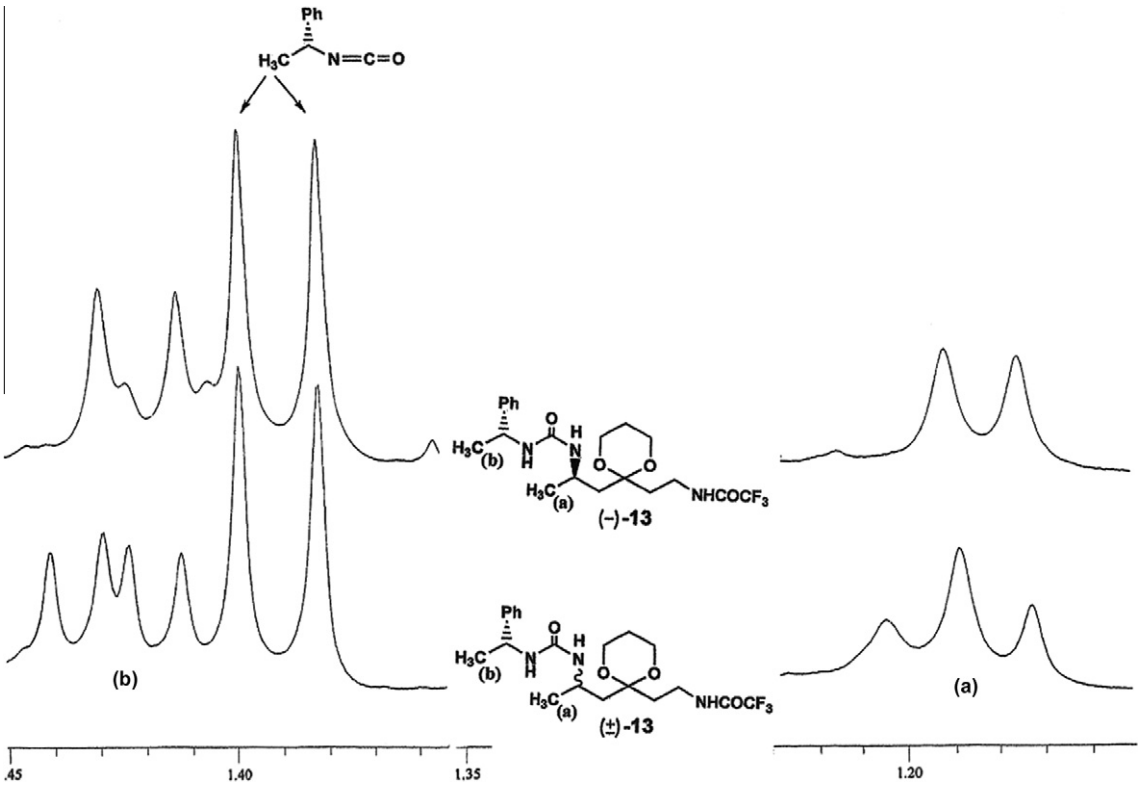
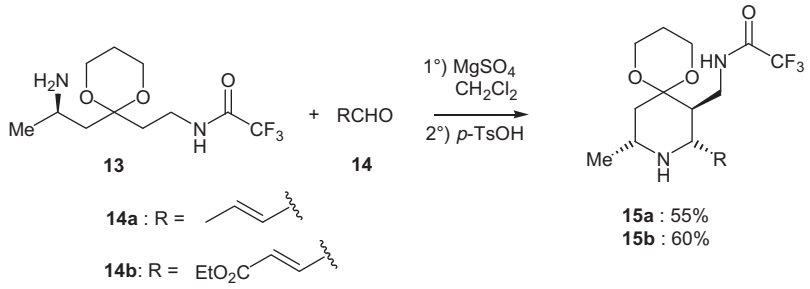
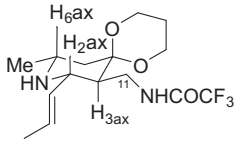


Figure 1. Determination of enantiomeric purity of amine **13** using chiral α-methylbenzyl isocyanate.



Scheme 4. Diastereoselective synthesis of the piperidines **15a** and **15b** by intramolecular Mannich reaction.

Table 1
Coupling constants for piperidine **15a**



15a

H_{2ax}	H_{3ax}	
$J_{H2ax\text{-}Heth}$ = 8.4 Hz	$J_{H3ax\text{-}H2ax}$ = 10.3 Hz	
$J_{H2ax\text{-}H3ax}$ = 10.3 Hz	$J_{H3ax\text{-}H11}$ = 7.8 Hz	
	$J_{H3ax\text{-}H11'}$ = 3.2 Hz	
H_{6ax}	H_{5ax}	H_{5eq}
$J_{H6ax\text{-}H5ax}$ = 11.9 Hz	$J_{H5ax\text{-}H5eq}$ = 13.3 Hz	$J_{H5eq\text{-}H5ax}$ = 13.3 Hz
$J_{H6ax\text{-}CH3}$ = 6.2 Hz	$J_{H5ax\text{-}H6ax}$ = 11.9 Hz	$J_{H5eq\text{-}H6ax}$ = 2.3 Hz
$J_{H6ax\text{-}H5eq}$ = 2.3 Hz		

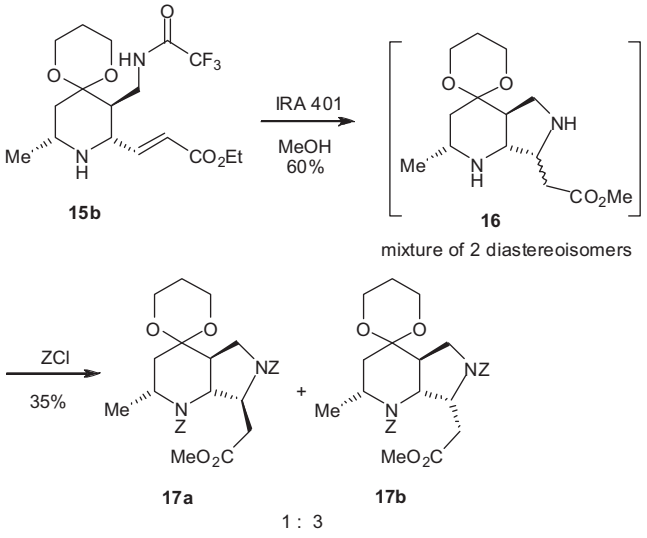
in a reproducible yield of 60%. Further aza-Michael addition of phthalimide upon **10** in the presence of Triton B® led to adduct **11** in 70% yield. Protection of the ketone as a dioxane followed by hydrazinolysis of the phthalimide moiety furnished the desired amine **12** in quantitative yield. Treatment of **12** with TFAA led to the trifluoroacetamide derivative which is deprotected by hydrogenolysis of the CBz appendage, realized with ammonium formate in the presence of palladium on charcoal in refluxing methanol,[6] to give amine **13**, which was prepared in eight steps starting from **7** in 32% overall yield.

We have checked the enantiomeric purity of diaminoketal **13** by ^{1}H NMR spectroscopy with α-methylbenzylisocyanate as the chiral derivative agent.[7] Comparison of signals obtained for both methyl groups in the racemic (±)-**13** and its isomeric (−)-**13** forms, demonstrated an excellent stereoisomeric ratio, proving that no racemisation occurred throughout the synthesis (Fig. 1).

Thus, condensation of amine (−)-**13** with aldehydes **14a,b** under conditions developed by our group (intramolecular Mannich type cyclisation)[8] gave the corresponding piperidines **15a** and **15b** as a single diastereomer (Scheme 4).[9]

As usual, the stereochemistry of piperidines **15** was confirmed by careful examination of the coupling constants between H_5/H_6 and H_2/H_3 (Table 1). For compound **15a**, the value of $^3J_{H2\text{-}H3}$ (10.3 Hz) proves that these two protons are in axial position, so, the two substituents on C-2 and C-3 are in a *trans* relative position. Moreover, the signal of H_6 shows a *trans* diaxial coupling constant with H_{5ax} (11.9 Hz) proving that the substituents of the piperidine on the C-2 and C-6 are in the *cis* position.[9] NMR spectra of piperidine **15b** present the same coupling constants for H_2, H_5 and H_6.

Treatment of **15b** with IRA 401 resin[10] in methanol led to the intramolecular condensation of α,β-unsaturated ester function, furnishing compound **16** as a mixture of diastereoisomers which could not be separated by column chromatography (Scheme 5). Transformation of this mixture to the di-CBz derivative gave the two diastereoisomers **17a** and **17b** which could be now separated albeit in poor yield.[11] The relative configurations of the stereogenic



Scheme 5. Synthesis of octahydro-2*H*-pyrrolo-[3,4-*b*]-pyridines **17**.

centres have been determined without any ambiguity by NOESY experiments.

We have thus developed an efficient route in order to obtain optically pure tri-substituted piperidines. This synthesis is based on an intramolecular Mannich type reaction and furnished an access to a stereoselective synthesis of octahydro-2*H*-pyrrolo-[3,4-*b*]-pyridine framework. Further applications and use of compounds **15** will be described in the near future.

Acknowledgment

We thank the Ministère de la Jeunesse, de l'Education Nationale et de la Recherche for financial support.

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9. *Piperidine* ***15a***: ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 5.62 (dq, 1H, *J* = 7.6, 15.3), 5.30 (dd, 1H, *J* = 8.4, 15.3), 4.10 (td, 1H, *J* = 2.3, 12.6), 4.00 (td, 1H, *J* = 2.3, 12.6), 3.85 (m, 2H), 3.57 (m, 1H), 3.48 (m, 1H), 3.19 (dd, 1H, *J* = 8.4, 10.3), 2.84 (dqd, 1H, *J* = 2.3, 6.2, 11.9), 2.78 (dd, 1H, *J* = 2.3, 13.3), 2.02 (m, 1H), 1.66 (d, 3H, *J* = 7.6), 1.52 (ddd, 1H, *J* = 3.2, 7.8, 10.3), 1.42 (m, 2H), 1.10 (d, 3H, *J* = 6.2), 1.02 (dd, 1H, *J* = 11.9, 13.3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ [156.6, 156.3] (q, *J* = 36), 131.6, 130.2, [117.7, 114.8] (q, *J* = 263), 99.6, 59.5, 59.3, 58.2, 48.1, 47.3, 37.1, 36.0, 25.6, 22.4, 18.0; HR-ESI-MS: calculated for $C_{15}H_{24}N_2O_3F_3$ $(M+H)^+$: 337.1739, found: 337.1737; $[\alpha]_D$ = +16.96 (c 1.025, $CHCl_3$). *Piperidine* ***15b***: 7.97 (s, 1H), 6.75 (dd, 1H, *J* = 8.6, 15.6), 5.94 (d, 1H, *J* = 15.6), 4.11 (q, 2H, *J* = 7.1), 4.01 (m, 2H), 3.86 (m, 2H), 3.49 (m, 2H), 3.40 (dd, 1H, *J* = 8.6, 11.0), 2.89 (dqd, 1H, *J* = 2.4, 6.2, 11.9), 2.80 (dd, 1H, *J* = 2.4, 13.5), 2.02 (m, 1H), 1.64 (ddd, 1H, *J* = 4.0, 7.4, 11.0), 1.57 (s, 1H), 1.44 (d, 1H, *J* = 13.9), 1.27 (t, 3H, *J* = 7.1), 1.10 (d, 3H, *J* = 6.2), 1.05 (dd, 1H, *J* = 11.9, 13.5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, [156.6, 156.3] (q, *J* = 36.2), 146.6, 124.7, [117.4, 114.8] (q, *J* = 263), 99.3, 60.7, 59.5, 59.4, 56.8, 47.7, 47.3, 37.0, 36.0, 25.5, 22.3, 14.3; HR-ESI-MS: calculated for $C_{15}H_{26}N_2O_5F_3$ $(M+H)^+$: 395.1794, found:395.1781; $[\alpha]_D$ = +37.8 (*c* 1.013, $CHCl_3$).
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11. *Compound* ***17a***: ^{1}H NMR (400 MHz, C_6D_6) δ 7.34–6.97 (m, 10H), 5.16–5.00 (m, 4H), 4.60 (m, 1H), 4.28 (dd, 1H, *J* = 7.2, 12.0), 4.15 (m, 1H), 4.03 (m, 1H), 3.97–3.86 (m, 2H), 3.80 (t, 1H, *J* = 14.6), 3.46–3.16 (m, 7H), 2.48 (td, 1H, *J* = 7.2, 12.0), 1.79 (d, 1H, *J* = 13.8), 1.57 (m, 1H), 1.33 (dd, 1H, *J* = 4.8, 13.8), 1.25 (m, 1H), 1.16 (d, 3H, *J* = 7.0), 0.56 (m, 1H); ^{13}C NMR (101 MHz, C_6D_6) δ 172.1, 156.4, 128.8, 128.6, 128.5, 128.4, 96.6, 67.2, 66.8, 60.3, 59.6, 59.2, 58.9, 50.9, 50.8, 49.8, 43.8, 37.0, 33.9, 25.5, 22.8; HR-ESI-MS: calculated for $C_{30}H_{36}N_2O_8Na$ $(M+Na)^+$: 575.2369, found: 575.2378; $[\alpha]_D$ = +85.2 (0.94, $CHCl_3$). *Compound* ***17b***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.28 (m, 10H), 5.26–4.99 (m, 4H), 4.88 (d, 1H, *J* = 6.9), 4.50 (m, 1H), 4.00 (t, 1H, *J* = 11.2 Hz,), 3.84 (m, 4H), 3.76 (dd, 1H, *J* = 6.8, 13.2), 3.69–3.50 (m, 5H), 2.74 (m, 1H), 2.43 (d, 2H, *J* = 14.5), 2.26 (dd, 1H, *J* = 7.4, 13.6), 2.01 (m, 2H), 1.35 (t, 4H, *J* = 7.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 156.5, 128.7, 128.5, 128.4, 128.3, 128.1, 128.0, 95.9, 67.9, 67.2, 66.9, 59.9, 59.6, 57.9, 55.4, 52.0, 49.2, 44.2, 42.6, 35.5, 35.0, 25.7, 23.2; HR-ESI-MS : calculated for $C_{30}H_{36}N_2O_8Na$ $(M+Na)^+$: 575.2369, found: 575.2388; $[\alpha]_D$ = −17.3 (0.46, $CHCl_3$).