Tetrahedron Letters 51 (2010) 4988–4990

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Simple and highly diastereoselective access to 3,4-substituted tetrahydro-1,8-naphthyridines from Morita–Baylis–Hillman adducts

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ARTICLE INFO

Article history:
Received 15 May 2010
Revised 10 July 2010
Accepted 13 July 2010
Available online 16 July 2010

ABSTRACT

We disclose herein a facile and straightforward method to access 3,4-substituted tetrahydro-1,8-naphthyridines from Morita–Baylis–Hillman. The strategy is based on a tandem sequence involving a Michael addition reaction followed by an intramolecular S_NAr reaction on a silylated-Morita–Baylis–Hillman adduct. In a single step, a new cycle is formed and the relative stereochemistry of two new centers is controlled with good to excellent diastereoselectivity.

1,8-Naphthyridine skeletons are present in many natural and synthetic compounds (Fig. 1). 1,8-Naphthyridine derivatives possess a large range of interesting biological activities and can potentially be used to treat infections,[1] atherosclerosis and hyperlididemia,[2] osteoporosis,[3] and malaria.[4] Besides, these compounds also exhibit anti-inflamatory,[5a,b] analgesic,[5a] anticancer,[5c] anti-hypertensive,[5e] and anti-diuretic[5g] activities.

Several synthetic approaches have been developed to form the naphthyridine ring.[6] Among naphthyridines, 1,2,3,4-tetrahydro-1,8-naphthyridine derivatives are of great pharmaceutical importance,[3c] since several drugs possess this backbone. Yet, very few procedures have been reported for the synthesis of such compounds. The usual route involves a regioselective hydrogenation of naphthyridines which are prepared via a Skraup[7] or a Friedländer reaction.[8] An optimized intramolecular Chichibabin reaction was also applied to access these bicyclic heterocycles.[9] Tin-free radical cyclizations have also been used as strategy to afford tetrahydronaphthyridines.[10]

Morita–Baylis–Hillman (MBH) reaction is a green atom-efficient condensation reaction, which allows the access to synthetically useful multifunctionalized small molecules.[11–13] MBH adducts have already been used as substrates for the preparation of 1,8-naphthyridine skeletons.[14] Basavaiah and Reddy reported an elegant strategy to prepare 1,8-naphthyridines from a 2-nitro cyanoacrylate.[14a] Su et al.[14b] also used an acetylated MBH adduct derived from 2-chloro pyridine-3-carboxaldehyde as a substrate for the syntheses of 1,8-naphthyridine skeleton.

In an ongoing medicinal chemistry research program aiming at the synthesis of new compounds for antitumoral biological screening, we needed to synthesize some 3,4-substituted tetrahydro-1,8-naphthyridines. We planned to add oxygenated functions in the 3,4-positions in order to improve pharmacokinetic profiles.[15]

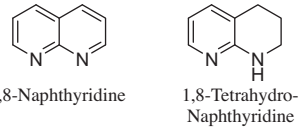

Figure 1. Naphthyridine skeletons.

In this Letter we disclose a facile and diastereoselective method to prepare 3,4-substituted tetrahydro-1,8-naphthyridine derivatives. Our approach is based on a tandem sequence involving a Michael addition reaction and an S_NAr reaction, which in a single step forms a cycle and controls the relative stereochemistry of two centers.

MBH adducts **6–9** were prepared using a reported protocol.[16] In brief, 2-chloro-3-pyridine carboxaldehyde and 2-chloro-3-quinolinecarboxaldehyde aldehyde were reacted with methyl or ethyl acrylate and acrylonitrile to provide the corresponding MBH adducts in good yield. Table 1 summarizes the results.

The elimination step during amine-conjugated addition on MBH adduct double bond had to be avoided. We hoped to use an experimental protocol similar to that employed by Su,[14b] however acetylated-MBH adducts were not allowed since they are prone to elimination through an S_N2' mechanism.

Some years ago, we[17] and Bouzide,[18] have demonstrated the effect of silylated-protecting groups on the diastereoselectivity of heterogeneous hydrogenation of MBH reactions. Perlmutter has observed the same effect when N-nucleophiles were added to the double bond of MBH adduct on a Michael reaction, and detected no trace of the elimination product.[19] In both cases, the *syn* diastereoisomer was largely and preferentially formed.

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† Joel Smith was an undergraduate American student, who participated on the NSF/Fapesp Program during winter 2009.

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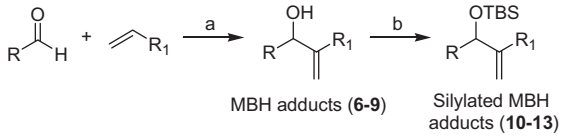
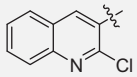
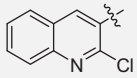
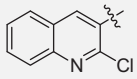
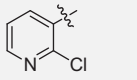
doi:10.1016/j.tetlet.2010.07.069

Table 1
Preparation and silylation of the MBH adducts



Reagents and conditions: a. acrylate, DABCO, ultrasound; b. TBSOTf, Et_3N, CH_2Cl_2, r.t.

Entry	R	R_1	Adduct[a,b] (%)	Silylated adducts[c] (%)
1		CO_2Me	**6**, 85	**10**, 100
2		CN	**7**, 71	**11**, 83
3		CO_2Et	**8**, 87	**12**, 93
4		CO_2Et	**9**, 87	**13**, 92

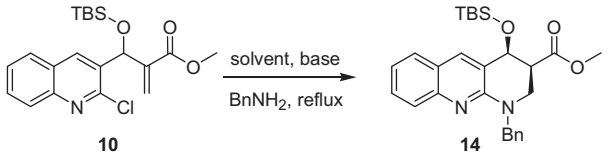
[a] Yields refer to isolated and purified products.
[b] Reactions were carried out with an excess of acrylate using ultrasound radiation.
[c] TBSOTf was used as silylating agent (see Supplementary data for experimental details).

The MBH adducts (**6**–**9**) were reacted with TBS triflate to afford the corresponding silylated derivatives (**10**–**13**) in excellent yields (Table 1).

Solutions of the MBH adduct **10** in toluene or dichloromethane were then initially treated with a tiny excess of benzylamine in the presence of triethylamine as a base. But unfortunately, this procedure failed to form **14** (Table 2, entries 1 and 2). We decided therefore to increase the polarity of the reaction medium. When an acetonitrile solution of **10** was treated under the same conditions as before, the desired naphthyridine **14** was formed but in very poor yield (Table 2, entry 3). To increase even more the polarity, acetonitrile was replaced by methanol, and fortunately now the 3,4-substituted 1,8-naphthyridine **14** was obtained in 48% yield and excellent *syn* diastereoselectivity (*syn*/*anti* 34:1) (Table 2, entry 5).

To improve the yield, several experimental modifications were tested without success such as higher temperatures, use of microwave or ultrasound radiation, and increased Et_3N concentration.

Table 2
Optimizing conditions to synthesize 1,8-naphthyridines



10 **14**

Entry	Base	Solvent	Yield[a] (%)
1	Et_3N	CH_2Cl_2	—[b]
2	Et_3N	Toluene	—[b]
3	Et_3N	CH_3CN	7
4	Et_3N	CF_3CO_2H	38
5	Et_3N	MeOH	48[c]
6	K_2CO_3	MeOH	9
7	NaOAc	MeOH	12

[a] Yields refer to isolated and purified products.
[b] Partial recovery of the starting material was possible.
[c] Diastereoselectivity was determined by ^1H NMR of the crude mixture.

Using these preliminary optimizing experimental conditions, the synthetic route was pursued further.

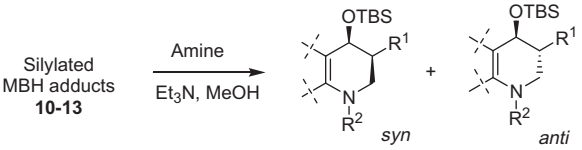
Several substituted 1,8-naphthyridines were easily obtained in moderate to good yield and good to excellent stereoselectivity (Table 3). For the cases where esters are the substituents, we rationalize that the diastereoselectivity results from the control exerted by the voluminous silyl group. Previous results support this proposition (**14a**, Fig. 2).[17,18]

Curiously, an inversion on the relative stereochemistry was observed when ester groups were replaced by cyano groups. A conformational analysis indicates that **20a** is the most stable conformer of the aza-enol formed as an intermediate in the Michael addition step.[17] Protonation also occurs on the bottom face (opposite of TBS) leading now preferentially to the *anti* diastereoisomer (Fig. 2).

The relative stereochemistry of both isomers was confirmed by NOE experiments. For instance, irradiation of compound **16** at 4.95 ppm (doublet absorption attributed to the carbinolic hydrogen—*syn* isomer) shows an increment of 3.9% on the absorption at 2.96 ppm, attributed to the hydrogen α carbonyl (see Supplementary data for details).

In summary, we have demonstrated that 3,4-substituted 1,8-naphthyridines can be prepared in moderate yields with a high

Table 3
3,4-Substituted 1,8-naphthyridines from MBH adducts



Entry	Silylated MBH adducts	R^1	R^2	Yield[a] (%)	Products; *syn*/*anti* ratio[b]
1	**10**	CO_2Me	Allyl	42	**15**, 13:1[c]
2	**10**	CO_2Me	$(CH_2)_3CO_2H$	61	**16**, 16.5:1
3	**10**	CO_2Me	$(CH_2)_2C_6H_4OCH_3$	66	**17**, 19:1
4	**10**	CO_2Me	$(CH_2)_2$Indoyl	63	**18**, 26:1
5	**10**	CO_2Me	H	79	**19**, 26:1
6	**11**	CN	$(CH_2)_2$Indoyl	26[d]	**20**, 1:22
7	**11**	CN	$(CH_2)_2C_6H_4OCH_3$	33[d]	**21**, 1:6
8	**12**	CO_2Et	$(CH_2)_2$Indoyl	54	**22**, 27.5:1
9	**13**	CO_2Et	$(CH_2)_2$Indoyl	24[d]	**23**, 6:1
10	**13**	CO_2Et	$(CH_2)_2C_6H_4OCH_3$	45	**24**, 12:1

[a] Yields refer to isolated and purified products.
[b] Diastereoselectivity was determined by ^1H NMR, by measuring the coupling constant of the carbinolic proton. For the *syn* isomer *J* is 1.8 Hz, while for the *anti* isomer *J* 5.0–6.0 Hz.
[c] See Supplementary data for experimental details.
[d] For entries 7, 8, 10 we observe a product degradation during isolation and purification.

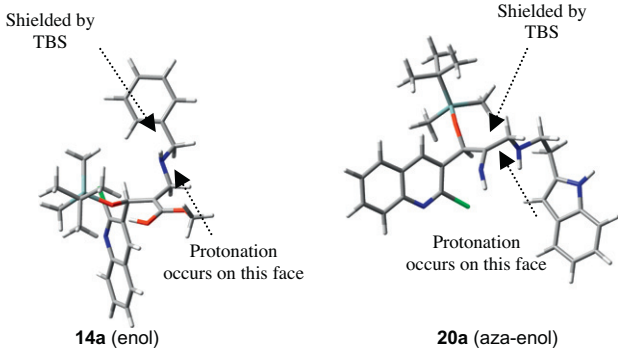


Figure 2. Protonation steps after Michael addition reaction.[20]

diastereoselectivity from MBH adducts. The method is very simple and allows the preparation of 1,8-naphthyridines in only three steps. In the last tandem step the heterocycle ring is formed with relative stereochemical control of two stereogenic centers.[21] These compounds are under biological screening in order to evaluate their antitumoral activity. Further studies are ongoing aiming to determine the wide range scope of this strategy.

Acknowledgments

We thank CNPq for fellowships to J.C.G. and F.C. and Fapesp for fellowship to M.T.R. Jr. We thank Ms. Marco Antônio Barbosa Ferreira for helping us on conformational analysis and Professor C.H. Collins for English revision of this manuscript.

Supplementary data

Supplementary data (experimental procedures as well as NMR data (^{1}H- and ^{13}C-) for all synthesized compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.069.

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20. The conformational analysis was performed running the Spartan Plus program (Spartan Plus, Wavefunction, Inc., Irvine, CA) using the MMFF field force. The selected low energy structures were re-optimized using a HF/3-21 g ab initio method (GAUSSIAN 03 program).
21. The same sequence was carried out with a deprotect MBH adduct, however a poor stereoselectivity was observed (2:1, *anti*/*syn*).