Synthesis of 1-tetrazolyl-1,2,3,4-tetrahydroisoquinoline bound-type *bis*-heterocycles via oxidative-Ugi-azide

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Abstract: A series of three novel 1-tetrazolyl-1,2,3,4-tetrahydroisoquinolines were synthesized in moderate yields (42-60%) via two-step process. The first one involved a NH-CH_2 bond oxidation of the 1,2,3,4-tetrahydroisoquinoline to give the corresponding imine using IBX as oxidant. The second step was an oxidative-Ugi-azide reaction from 3,4-dihydroisoquinoline, $TMSN_3$ and the corresponding isocyanides as starting reagents.

Keywords: 1-tetrazolyl-1,2,3,4-tetrahydroisoquinolines; Ugi oxidative, IBX, bound-type *bis*-heterocycles, oxidative-Ugi-azide.

Introduction

1,2,3,4-tetrahydroisoquinoline is a privileged scaffold in medicinal chemistry because it is present in several compounds exhibiting biological activity, for example hemostatics, antiamoebics, antihypertensives, and antiparasitics.[1] In the same context, it is the core of a wide variety of naturals products (**Fig. 1**). On the other hand, The 1,5-DS-T are known as bioisosters of the *cis*-amide bond of peptides by adopting their effective biological conformations. Thus, there are many bioactive compounds having the 1,5-DS-T moiety, for example, vasorelaxants, antiallergics, diuretics, and thrombogenesis inhibitors.[2]

Bis-heterocycles are a special class of molecules formed by two heterocyclic moieties in linked, spaced, fused, merged or bound manner,[3] which have high interest to synthetic chemists because have proven to be useful in various fields such as agrochemistry, optics, material-polymer science, and mainly in medicinal chemistry.[4] There are a few reports in the literature describing the synthesis of bound-type *bis*-heterocycles based on the tetrahydroisoquinoline moiety.[5] Besides, there are also few reports describing the synthesis of *bis*-heterocycles based on the 1,5-DS-T via Ugi-azide[6,7] (**Fig. 1**).

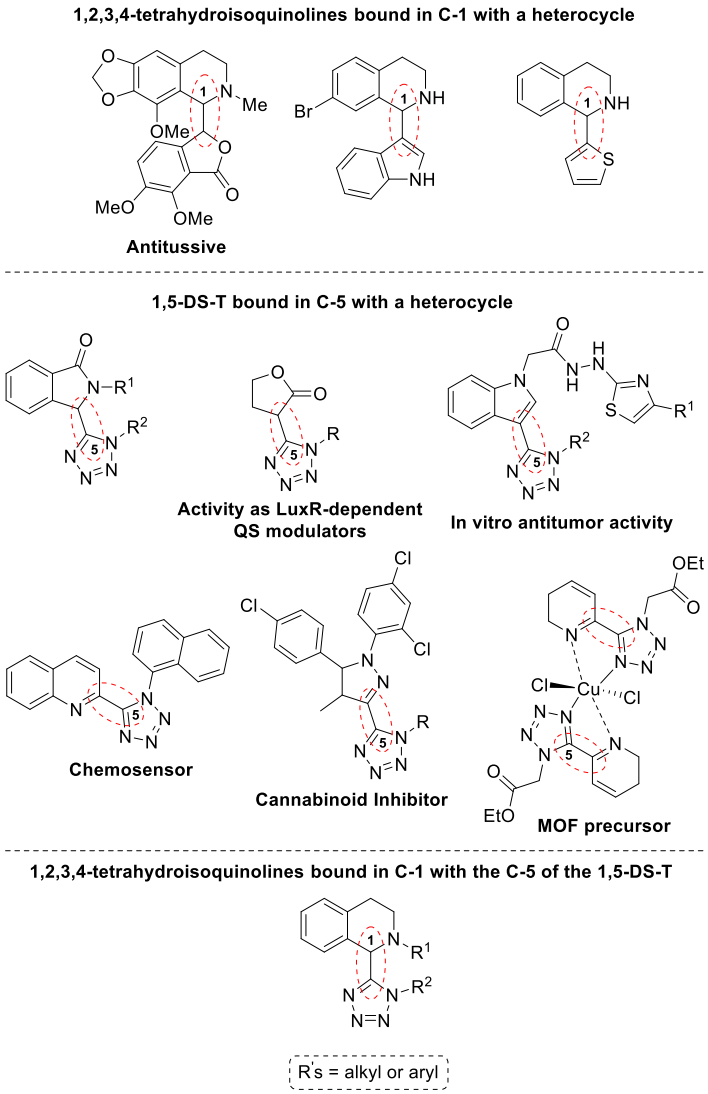


Figure 1. Bound-type *bis*-heterocycles

A few examples of the oxidative Ugi-type MCR have been reported.[8] Secondary amines are oxidized into their corresponding imines, which subsequently follow the Ugi reaction mechanism. Nicolaou reported the use of IBX as oxidant of secondary amines to imines.[9] Then, Zhu used this methodology to report the first IBX-promoted oxidative Ugi-type reaction toward a variety of tetrahydro-isoquinolines.[10]

The use of cyclic imines in the Ugi-azide reaction has been little explored. Nenajdenko is a pioneer in developing Ugi-azide reactions using α-substituted cyclic imines for the synthesis of 1,5-DS-T.[11]

Results and Discussion

There are few reports in the literature describing the synthesis of bound-type *bis*-heterocycles having the 1,2,3,4-tetrahydroisoquinoline moiety bound in C-1 with the C-5 of the 1,5-DS-T. Soeta reported a MCR between isocyanides and C,N-cyclic N'-acyl azomethine imines using TMSCl and NaN_3 for preparing 16 new examples in 64 to 99% yields.[12] Besides, Shinde reported a four-component reaction between 2-(2-bromoethyl)benzaldehyde, isocyanides, amines, and sodium azide to synthesize 15 new examples in 72 to 99% yields.[13] In this work, we describe the synthesis of three new 1-tetrazolyl-1,2,3,4-tetrahydroisoquinoline via amine oxidation promoted by IBX, and a further oxidative Ugi-azide reaction. As seen, the nitrogen of the 1,2,3,4-tetrahydroisoquinoline moiety is NH, which could be used for further processes based on secondary amines. Soeta and Shinde synthetic methods gave THIQ substituted in N-2. As seen, our work is a contribution in the synthesis of bound-type *bis*-heterocycles via one pot multicomponent-based processes, specially via oxidative Ugi-azide reaction (**Fig. 2**).

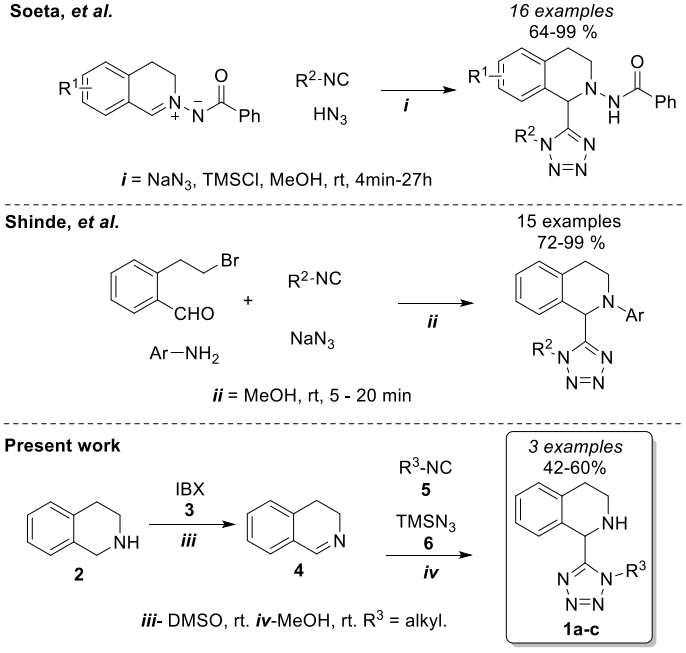


Figure 2. Synthesis of bound-type THIQ-T *bis*-heterocycles

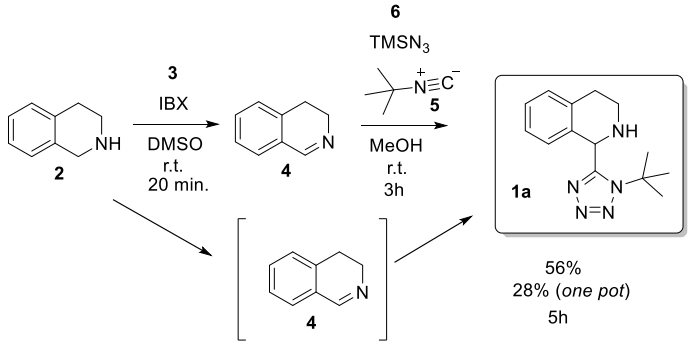
The first step involved a NH-CH_2 bond oxidation of the 1,2,3,4-tetrahydroisoquinoline (**2**) to afford the 3,4-dihydroisoquinoline (**4**) using IBX (**3**) as oxidant and DMSO [1.0 M] as solvent in 20 min. (quant yield). The second step was an Ugi-azide reaction between the 3,4-dihydroisoquinoline (**4**), the corresponding isocyanide (**5**) and the $TMSN_3$ (**6**) in MeOH [1.0 M] as solvent at room temperature for 3 hours to give the corresponding products **1a-c** (**Table 1**). It is noteworthy that the highest yields were observed when aliphatic isocyanides were used (**Table 1**, entries 1 and 2).

Table 1. Synthesis1-tetrazolyl-1,2,3,4-tetrahydroisoquinolines

Entry[a]	R	Yield (%)[b,c]
1	*t*-Bu	56
2	Cy	60
3	Bn	42

[a] Reaction conditions: Imine **4** (1 equiv.), isocyanide **5** (1 equiv.), $TMSN_3$ **6** (1 equiv.). MeOH [1.0 M].
[b] Product characterized by ^1H NMR and ^{13}C NMR.
[c] Isolated yields after column chromatography.

These results are consistent with the nucleophilic nature of isonitriles described by Mayr,[14] being more nucleophilic aliphatic isocyanides, followed by benzyl (Table 1). To gain scope, the reaction was carried out under *one pot* process using *tert*-butyl isocyanide as starting reagent, but the product **1a** was obtained in 28% yield (**Scheme 1**). This yield may seem lower, but, it is important to highlight the number of formed bonds in one step and the molecular complexity of product **1a**.



Scheme 1. One pot synthesis of **1a**

Conclusions

The oxidation of secondary amines toward imines gave higher yields, which could be considered to avoid the inherent difficulties for synthesizing Schiff bases from inactivated aldehydes and anilines. Oxidative Ugi-azide reaction gave good overall yields in the two steps. The one pot version was performed in lower yield. An extension of this work is being carried out using alternative heat sources (like MW and ultrasound), even to gain substrate scope. It is noteworthy that *bis*-heterocycles herein described may find application in medicinal chemistry because they are formed by two heterocyclic (THIQ and 1,5-DS-T) moieties present in a wide range of bioactive compounds and drugs.

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Experimental

General Information, software, instrumentation and chemicals

^{1}H and ^{13}C NMR spectra were acquired on Bruker Advance III spectrometer (500 MHz). The solvent for NMR samples was $CDCl_3$. Chemical shifts are reported in parts per million (δ/ppm). Internal reference for NMR spectra is TMS at 0.00 ppm. Coupling constants are reported in Hertz (*J*/Hz). Multiplicities of signals are reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). NMR spectra were analyzed using the MestreNova software (version 6.0.2-5475). The reaction progress was monitored by TLC and the spots were visualized under UV light (254 or 365 nm). Flash column chromatography was performed using silica gel (230-400 mesh) and mixtures of Hexanes with AcOEt as mobile phase. Melting points were determined on a Fisher-Johns apparatus and were uncorrected. Commercially available reagents were purchased in Sigma-Aldrich and were used without further purification. Structure names and drawings were done using the ChemBioDraw Ultra software (version 13.0.0.3015).

Synthesis and characterization of the 3,4-dihydroisoquinoline (**4**): In a vial (10 ml), to a stirred solution of 1,2,3,4-tetrahydroisoquinoline (1.0 equiv.) in DMSO anhydrous [1.0 M] under nitrogen atmosphere, IBX (1.5 equiv.) were added carefully. The resulting mixture was stirred at room temperature for 20 minutes and then filtered to remove the solid IBX. Extractions (3 x 25 mL) with ethyl acetate and excess of brine were done. The compound imine **4** was isolated in quantitative yield as yellow oil. *Spectral data:* ^{1}H NMR (500 MHz; $CDCl_3$; TMS): δ 8.34 (s, 1H), 7.39-7.34 (m, 1H), 7.33-7.26 (m, 2H), 7.18-7.14 (m, 1H), 3.80-3.75 (m, 2H), 2.78-2.73 (m, 2H).

Synthesis and characterization of the 1 1-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)-1,2,3,4-tetrahydroisoquinoline (**1a**): In a vial (10 ml), to a stirred solution of 3,4-dihydroisoquinoline (**4**) (1.0 equiv) in MeOH anhydrous [1.0 M] under nitrogen atmosphere, *tert*-butylisocyanide (1.0 equiv.) and azidotrimethylsilane (1.2 equiv.) were added sequentially. Then, the reaction mixture was stirred at room temperature for 3 hours and the solvent was removed to dryness. The crude was extracted (3 x 25 mL) with AcOEt and excess of brine, then dried using sodium sulfate, filtered over celite pad and evaporated to dryness. The organic layer was purified by column chromatography using a mixture of Hexanes with AcOEt (7:3, v/v) to afford the product **1a** (56%) (or 28% in one pot manner from **2**) as pale yellow solid, R_f (Hex-

AcOEt 7/3 v/v) = 0.19, mp = 178-181. *Spectral data:* ^{1}H NMR (500 MHz; $CDCl_3$; TMS): δ 7.65-7.63 (m, 1H), 7.47-7.43 (m, 1H), 7.67-7.64 (m, 1H), 7.34-7.30 (m, 1H), 7.25-7.23 (m, 1H), 5.30-5.21 (m, 1H), 4.91-4.85 (m, 1H), 4.03-3.98 (m, 2H), 2.88-2.83 (m, 2H), 1.05 (s, 9H).

Synthesis and characterization of the 1-(1-cyclohexyl-1*H*-tetrazol-5-yl)-1,2,3,4-tetrahydroisoquinoline (**1b**): In a vial (10 ml), to a stirred solution of 3,4-dihydroisoquinoline (**4**) (1.0 equiv) in MeOH anhydrous [1.0 M] under nitrogen atmosphere, cyclohexyl isocyanide (1.0 equiv.) and azidotrimethylsilane (1.2 equiv.) were added sequentially. Then, the reaction mixture was stirred at room temperature for 3 hours and the solvent was removed to dryness. The crude was extracted (3 x 25 mL) with AcOEt and excess of brine, then dried using sodium sulfate, filtered over celite pad and evaporated to dryness. The organic layer was purified by column chromatography using a mixture of Hexanes with AcOEt (7:3, v/v) to afford the product **1b** (60%) as pale yellow solid, R_f (Hex-AcOEt 7/3 v/v) = 0.21, mp = 148-150. *Spectral data:* ^{1}H NMR (500 MHz; $CDCl_3$; TMS): δ 7.65-7.62 (m, 1H), 7.46-7.42 (m, 1H), 7.65-7.62 (m, 1H), 7.34-7.30 (m, 1H), 7.28-7.25 (m, 1H), 5.31-5.22 (m, 1H), 4.91-4.84 (m, 1H), 4.03-3.98 (m, 2H), 2.88-2.83 (m, 2H), 2.15-2.08 (m, 2H), 2.07-1.99 (m, 2H), 1.95-1.89 (m, 1H), 1.78-1.71 (m, 1H), 1.57-1.51 (m, 1H), 1.44-1.30 (m, 1H).

Synthesis and characterization of the 1-(1-benzyl-1*H*-tetrazol-5-yl)-1,2,3,4-tetrahydroisoquinoline (**1c**): In a vial (10 ml), to a stirred solution of 3,4-dihydroisoquinoline (**4**) (1.0 equiv) in MeOH anhydrous [1.0 M] under nitrogen atmosphere, benzyl isocyanide (1.0 equiv.) and azidotrimethylsilane (1.2 equiv.) were added sequentially. Then, the reaction mixture was stirred at room temperature for 3 hours and the solvent was removed to dryness. The crude was extracted (3 x 25 mL) with AcOEt and excess of brine, then dried using sodium sulfate, filtered over celite pad and evaporated to dryness. The organic layer was purified by column chromatography using a mixture of Hexanes with AcOEt (7:3, v/v) to afford the product **1c** (42%) as pale yellow solid, R_f (Hex-AcOEt 7/3 v/v) = 0.24, mp = 148-150. *Spectral data:* ^{1}H NMR (500 MHz; $CDCl_3$; TMS): δ 7.67-7.63 (m, 1H), 7.45-7.42 (m, 1H), 7.68-7.65 (m, 1H), 7.34-7.31 (m, 1H), 7.29-7.26 (m, 1H), 7.14-7.09 (m, 1H), 5.30-5.20 (m, 1H), 4.90-4.82 (m, 1H), 4.12 (s, 2H), 4.03-3.99 (m, 2H), 2.88-2.84 (m, 2H).

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