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Formation and reductive ring opening reactions of indolyl-isoxazolidines: access to novel natural product analogs and precursors

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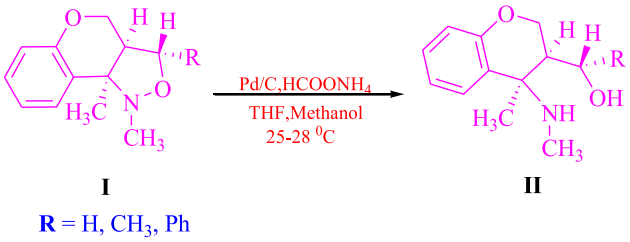
ABSTRACT

Regio- and stereoselective 1,3-dipolar cycloadditions of *C*-(3-indolyl)-*N*-phenylnitrone (**2**) with variedly substituted dipolarophiles were carried out to obtain *syn*- C4 and C5 substituted indolyl-isoxazolidines **6a–c** and **7a–f**, respectively. Reduction of obtained isoxazolidines, by employing various reducing agents, causes cleavage of the N–O bond, which is accompanied by concomitant cleavage of C–N bond leading to the formation of a library of novel indole based natural product analogs and precursors.

1. Introduction

1,3-Dipolar cycloaddition is a versatile tool in the hands of synthetic organic chemists to generate various biologically important target molecules and their precursors.[1] Notably, substituted isoxazolidines have been synthesized via 1,3-dipolar cycloadditions of nitrones with alkenes and are important precursors to β-amino acids,[2] β-lactams,[3] 1,3-amino alcohols,[4a] and pyrrolidinones[4b] obtained through reductive N–O bond cleavage. Earlier, we have reported the formation of conformationally constrained $\beta^{2,3,3}$–amino alcohols by reductive cleavage of the N–O bond of tricyclic isoxazolidines with ammonium formate in the presence of palladium on charcoal (Pd/C) or zinc-acetic acid (Scheme 1).[5a]

There are available various literature reports, where oxazolidinones have been subjected to reductive ring opening to get natural products, precursors for natural products and peptidomimetics.[5b–h]



Scheme 1.

On the other hand, the indole moiety is a prominent and privileged structural motif found in numerous natural products, metabolites, neurotransmitters and various synthetic compounds with interesting biological activities (Fig. 1). A large number of indole alkaloids are reported to possess cytotoxic, analgesic, anxiolytic, *anti*-inflammatory, and immunomodulating activities.[6a]

Inspired by reported significance of indole based scaffolds[6a] and in continuation of our previous work,[5a,6b] we have examined 1,3-dipolar cycloaddition reactions of *C*-(3-indolyl)-*N*-phenylnitrone with various dipolarophiles to obtain variously substituted indolyl-isoxazolidines; reductive cleavage of N–O bond of the obtained

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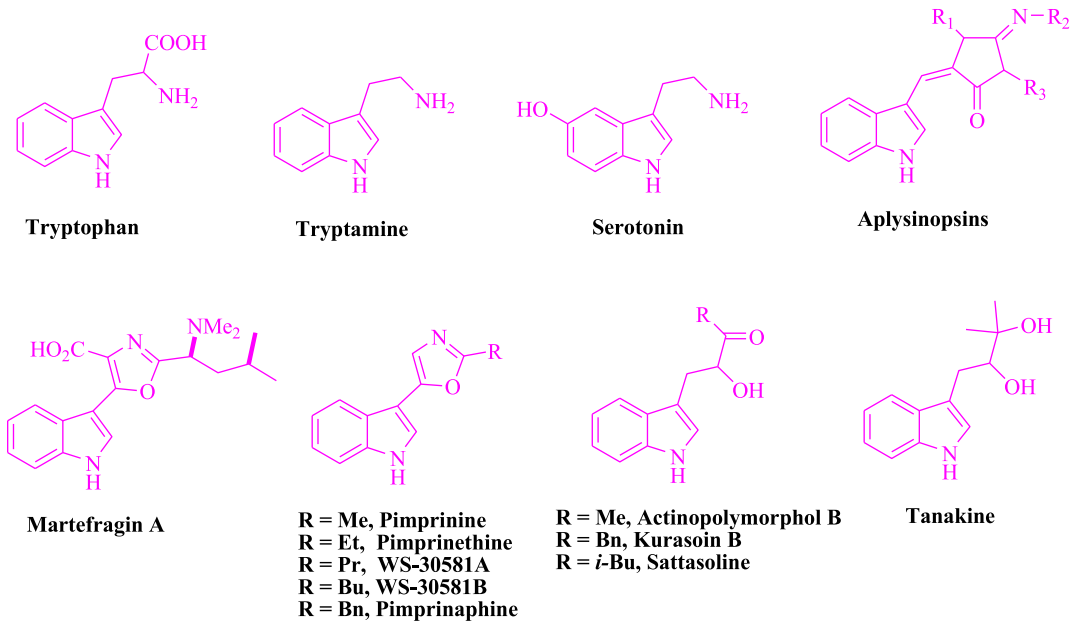

Fig. 1. Structures of some naturally occurring indoles.

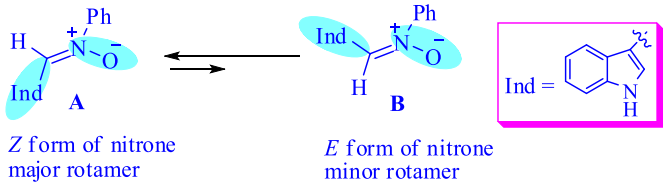

Fig. 2. *E* and *Z* conformations of nitrone **(2)**.

isoxazolidines was anticipated to furnish valuable precursors for the preparation of pharmaceuticals, natural products and peptidomimetic scaffolds.

2. Results and discussion

2.1. (a) Regio- and stereoselective 1,3-dipolar cycloadditions of C-(3-indolyl)-*N*-phenylnitrone (2) with variously substituted dipolarophiles (3–5)

Initially, the reactions of *C*-(3-indolyl)-*N*-phenylnitrone (**2**) with various monosubstituted and disubstituted dipolarophiles (**3a–f**, **4** and **5**) were carried out by irradiating equimolar amount of the addends in a focused monomode microwave reactor.[6] After completion of the reactions (monitored by TLC) the residues obtained were resolved by column chromatography over silica gel to obtain the cycloadducts **6–9**, which were characterized spectroscopically (^{1}H NMR, ^{13}C NMR and HRMS). The results are summarized in Scheme 2 and Table 1.

The assigned regiochemistry of addition in **6a–c** is based on ^{1}H NMR chemical shift of methylene-Hs (C5–Hs) located at δ 4.55–4.41 and this downfield shifted position in ^{1}H NMR is indicative of the attachment of methylene carbon to oxygen in **6a–c**. These conclusions are corroborated by the observed proton connectivities (couplings) and ^{13}C NMR chemical shift assignments, which clearly indicated that C4–H is vicinal to both C3–H and C5–Hs. The *syn*/*anti*-stereochemistry in **6a–c** involving indole group at C3 and the ester functionality at C4 of isoxazolidine ring is based on ^{1}H NMR couplings involving C3–H and C4–H, and follows from the premise that the *cis*-vicinal ^{1}H coupling constants are always higher than *trans* in case of isoxazolidines and related heterocycles.[7] Thus, for instance, in the case of **6b**, C3–H appeared as a doublet at δ 5.44 (J=8.6 Hz); the high value of $J_{3,4}$ alluded to *cis* arrangement. However, in the case of **7a–f**, ^{1}H NMR clearly indicated that the methylene hydrogens (C4–Hs) are coupled with both C3–H and C5–H, and is corroborated by ^{13}C chemical shifts of various carbons of isoxazolidine moiety. For instance, the ^{13}C NMR resonance of methylene carbon (C4) in **7a–f** appeared in the range δ 37–45, clearly indicating that it is not attached to oxygen. The assigned stereochemistry in cycloadducts (**7a–f**) is also based on NMR spectral evidence. The *syn* relationship between indole moiety at C3 and various substituents at C5 in **7a–f** are based on ^{1}H NMR couplings involving C3–, C4– and C5–Hs and followed from the consistent observation[6,7b–d,8] that the *cis* vicinal ^{1}H coupling are always higher (5–9 Hz) than the *trans* (0–6 Hz) in case of isoxazolidines. For instance, in compound **7f** the values of coupling constants $J_{3,4a}$=8.2 Hz, $J_{3,4b}$=5.4 Hz, $J_{5,4a}$=7.5 and $J_{5,4b}$=4.2 Hz, indicated that both C3–H and C5–H shows higher coupling and hence *cis* relationship with C4–Ha, thereby, establishing a *cis* relationship between C3–H and C5–H.

The formation of cycloadducts **6a–c** as minor regioisomer of addition can be rationalized in terms of the frontier molecular orbital controlled cycloaddition involving HOMO (dipole)-LUMO (dipolarophiles) interaction.[6,9] To rationalize the effect of 3-indolyl moiety on the molecular orbitals of 1,3-dipole, the DFT (Density functional theory) calculations were performed using GGA-DFT package DMol-3[6d,e] on *C*-(3-indolyl)-*N*-phenylnitrone (**2**), α,*N*-diphenyl nitrone (**2A**) and *C*-(chrom-4-one-3-yl)-*N*-phenylnitrone (**2B**) in *Z* conformation, whose cycloaddition reactions have been reported by us earlier (Table 2).[6b,c,10] The calculations revealed that nitrone **2** has high lying HOMO as compared to other nitrones **2A** and **2B**. Therefore, formation of 4-substituted regioisomer is obtained even with less electron deficient dipolarophiles. Normally, 4-substituted isoxazolidines are obtained in reactions involving highly electron deficient dipolarophiles such as nitro-olefins,[9] wherein HOMO (dipole)-LUMO (dipolarophiles) interaction intervenes, however, in the case of relatively electron rich dipoles having a high lying HOMO result in obtaining of 4-regioisomers even with less electron deficient dipolarophile such as acrylates.