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LETTER ARTICLE

Synthesis of *trans* N-Substituted Pyrrolidine Derivatives Bearing 1,2,4-triazole Ring

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Abstract: ***Background*:** 1,2,4-triazoles scaffolds display significant biological activities due to hydrogen bonding, solubility, dipole character, and rigidity.

***Objective*:** The core motif of 1,2,4-triazoles plays a vital role in clinical drugs such as Rizatriptan (anti-migraine), Ribavirin (antiviral), anastrozole (anticancer), etizolam (anxiolytic), estazolam (anticonvulsant), alprazolam (anti-hypnotic), letrozole (aromatase inhibitor), loreclezole (anticonvulsant), trazadone (antidepressant) *etc*.

***Methods*:** Epoxide ring opening of tert-butyl 6-oxa-3-azabicyclo [3.1.0] hexane-3-carboxylate followed by methylation under basic conditions and de-protection gave the corresponding trans 1-(4-methoxypyrrolidin-3-yl)-1H-1,2,4-triazole hydrochloride salt as the precursor. This precursor on reaction with substituted benzoyl chlorides and benzyl bromides gave the desired amide and amine products.

***Results*:** A library of 14 N-substituted pyrrolidine derivatives *i.e*. trans3-methoxy-4-(1H-1,2,4-triazol-1-yl) pyrrolidin-1-yl) (phenyl)methanone and trans 1-benzyl-4-methoxypyrrolidin-3-yl)-1H-1,2,4-triazole were prepared.

***Conclusion*:** Eight novel amides (6a-h) and six amines (8a-f) derivatives were synthesized using 1-(4-methoxypyrrolidin-3-yl)-1H-1,2,4-triazole 4 salt with substituted benzoyl chlorides and benzyl bromides.

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1. INTRODUCTION

1,2,4-triazoles are the most important scaffolds having significant biological activities because of their hydrogen bonding, solubility, dipole character, and rigidity. The core motif of 1,2,4-triazoles plays a vital role in clinical drugs such as Rizatriptan [1] (anti-migraine), Ribavirin [2] (antiviral), anastrozole [3] (anticancer), etizolam [4] (anxiolytic), estazolam [5] (anticonvulsant), alprazolam [6] (anti-hypnotic), letrozole [7] (aromatase inhibitor), loreclezole [8] (anticonvulsant), trazadone [9] (antidepressant) *etc*. (Fig. **1**).

Most of the 1,2,4-triazole pharmacophores such as voriconazole, fluconazole, ravuconazole, posaconazole [10], cyproconazole, epoxyconazole, m*etc*onazole, propiconazole, prothioconazole, triadimefon, tebuconazole and triadimenol [11] belong to a class of drugs called azole antifungals.

1,2,4-triazoles and their derivatives have been shown excellent biological activity in γ-aminobutyric acid-A (GABA-A) receptors [12], anticonvulsant [13], anti-urease [14], antimalarial [15], antioxidant [16], antiviral [17], PDE4A inhibitors [18], neuroprotectant [19], and antileishmanial [20]. They have also shown importance in material science [21].

Previously, chemoenzymatic synthesis was carried out by ring-opening of epoxide using 1,2,4 triazole in a non-selective fashion with high levels of stereoselectivity [22]. (Scheme **1a**). Enantio-selective syntheses of carbocyclic ribavirin also

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involve regioselective ring-opening of chiral epoxide by using 1,2,4 triazoles as a key step [23] (Scheme **1b**).

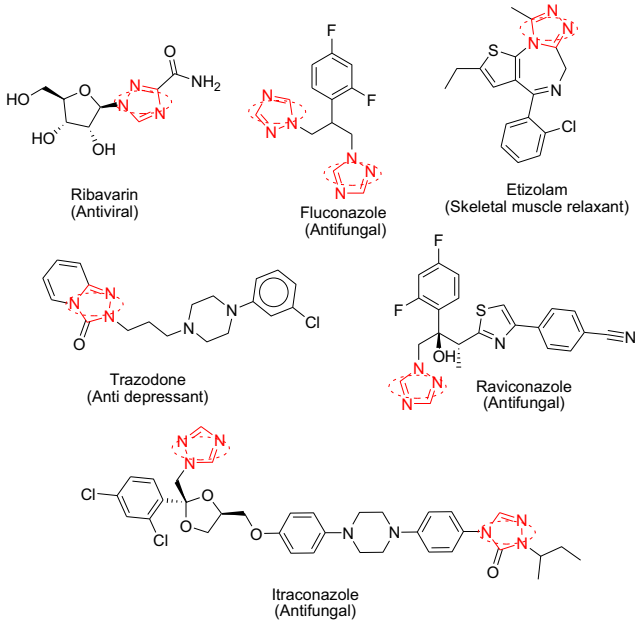
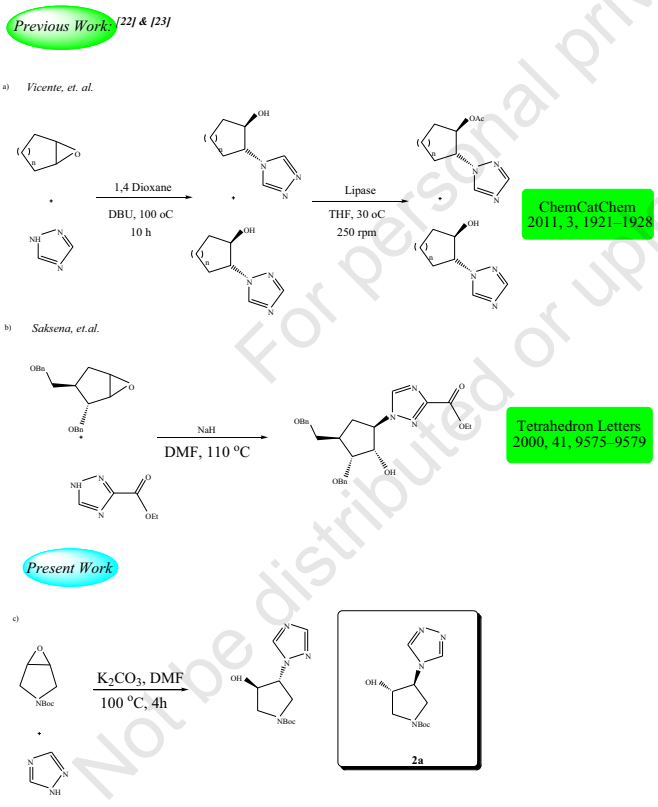


Fig. (1). Natural products having 1,2,4 triazole ring with biological activities



Scheme 1. Epoxide opening using 1,2,4 triazole.

In continuation of our research interest in Heterocyclics [24a-d], Spirocyclics [24e-h], and Bioactive Skeletons [24i-l], we have carried out the synthesis of *trans*-racemic 1-(4-methoxypyrrolidin-3-yl)-1H-1,2,4-triazole derivatives as amides, and amines.

2. MATERIALS AND METHODS

All reactions were carried out with dry, freshly distilled solvents in anhydrous conditions. THF was distilled from sodium, while dichloromethane was distilled from CaH^2 immediately prior to use. Thin-layer chromatography (TLC) was performed on silica gel plates (60F-254) using UV-light (254 and 365 nm). Flash chromatography was performed on silica gel (230– 400 mesh). NMR (400 MHz for 1H NMR, and 13C NMR) spectra were recorded in CDCl3 with TMS as the internal standard. Chemical shifts are reported in ppm, and coupling constants are given in Hz. Data for 1H NMR are recorded as follows: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, dd, doublet of doublet), coupling constant (Hz), integration. Data for 13C NMR are reported in terms of chemical shift (δ, ppm).

3. EXPERIMENTAL

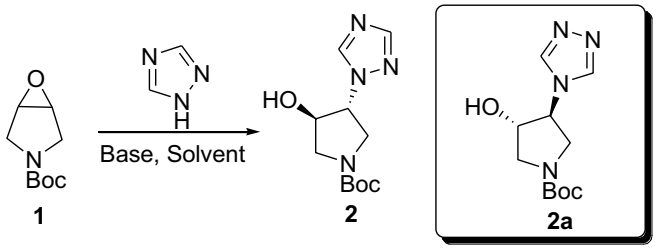
For the synthesis of trans-(racemic) tert-butyl 3-hydroxy-4-(1H-1,2,4-triazol-1-yl) pyrrolidine-1-carboxylate (2), DMF (100 mL) K^2CO^3 (0.13 mol) was added to a solution of tert-butyl 6-oxa-3-azabicyclo [3.1.0] hexane-3-carboxylate 1 (10.0 g, 0.05 mol), followed by 1,2,4-triazole (0.11 mol), at 20 °C. Then the reaction mixture was heated to 100 °C and maintained for 4 h. After completion of the reaction on TLC, the reaction mixture was quenched with ice-cold water (200 mL) and diluted with ethyl acetate (300 mL). The organic layer was washed with water (2 X 100 mL), followed by brine solution. The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford trans-(racemic)-tert-butyl 3-hydroxy-4-(1H-1,2,4-triazol-1-yl) pyrrolidine-1-carboxylate 2 (11.7 g, 75%) as Colorless gummy liquid.

4. RESULTS AND DISCUSSION

Our experiment, began with commercial available *tert*-butyl 6-oxa-3-azabicyclo [3.1.0] hexane-3-carboxylate **1** and 1,2,4 triazole (Table **1**). Initially, ring-opening of epoxide **1** using 1,2,4-triazole as a nucleophile was carried out in an inorganic base, *i.e.*, Na_2CO_3 at 20 °C (entry 1**,** Table **1**) using methanol-water solvent mixture did not give the desired product **2**. The reaction carried out using K_2CO_3 in methanol gave the 45% yield (entry 2**,** Table **1**). Changes in the base, such as cesium carbonate in THF solvent, decrease the yield to 20% (entry 3**,** Table **1**). Change from inorganic to organic base, *i.e.*, Triethylamine reaction extended for 36 hours, yielded the same result (entry 4, Table-1) The yield was 37 percent when sodium acetate was used in the presence of a 1,4-dioxane-water solvent mixture at 80°C for 24 hours (entry 5, Table **1**). The yield was slightly increased in the presence of ethanol solvent under the same base in 48% (entry 6**,** Table **1**). The use of polar aprotic solvents like acetonitrile gave a 64% yield (entry 7**,** Table **1**). Polar solvents like methanol and DMA gave 55 and 74% yield, respectively (entry 8, 9 Table **1**). Increasing temperature at 100 °C Use of polar aprotic solvent like DMF gave 80% yield (entry 10**,** Table **1**) (Scheme **1**). The epoxide ring opening of compound **1** with 1,2,4-triazole (step-1) is a highly challenging reaction because of its region-selectivity between compounds **2** and **2a**.

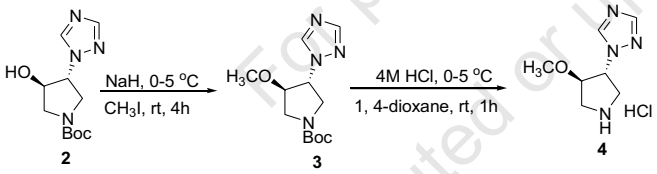
Finally, we achieved a high yield single regioisomer tert-butyl -3-hydroxy-4-(1H-1,2,4-triazol-1-yl) pyrrolidine-1-carboxylate as trans-racemic to avoid the formation of **2a** (Table **1**).

Table 1. Optimization of reaction conditions [a].



Entry	Base	Solvent	Temp/Time	Yield[b]
1	Na_2CO_3	MeOH/H_2O	20 ºC/24h	NA
2	K_2CO_3	MeOH	20 ºC/24h	45
3	Cs_2CO_3	THF	20 ºC/24h	20
4	Et_3N	THF	20 ºC/36h	20
5	NaOAc	1,4-dioxane/H_2O	80 ºC/24h	37
6	K_2CO_3	EtOH	20 ºC/24h	48
7	K_2CO_3	acetonitrile	20 ºC/24h	64
8	K_2CO_3	MeOH	60 ºC/12h	55
9	K_2CO_3	DMA	100 ºC/8h	74
10	K_2CO_3	DMF	100 ºC/4h	80

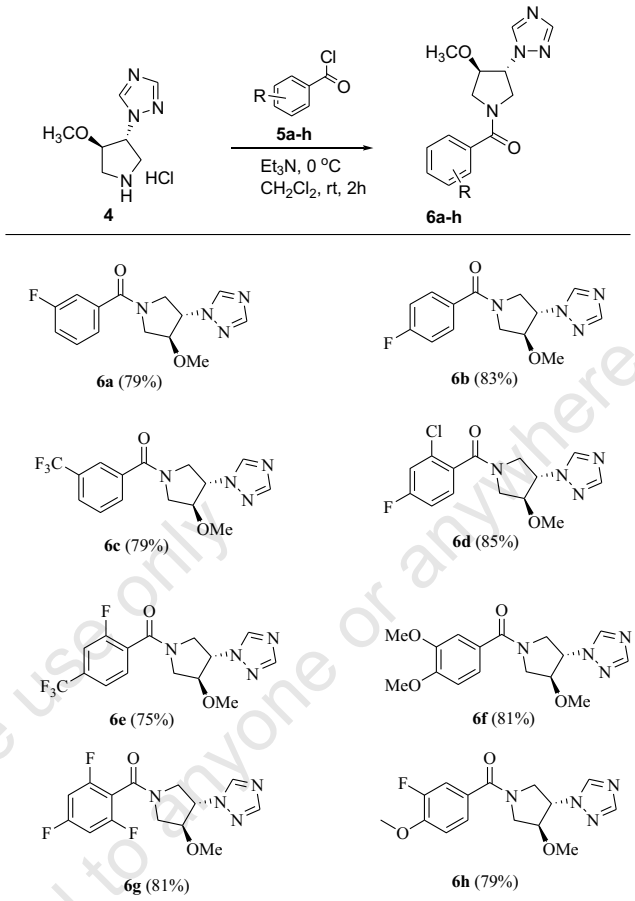
[a] All the reactions were performed by using 1 (0.016 mmol) and 1,2,4 triazole (0.017 mmol) using 0.04 mmol of base in THF (1.0 ml). [b] Isolated yield of 2 after column chromatography.



Scheme 2. Synthesis of *trans*1-(4-methoxypyrrolidin-3-yl)-1H-1,2,4-triazole hydrochloride salt **4**.

To synthesize main precursor **4** as the hydrochloride salt, compound **2** was treated with methyl iodide to get the methoxy derivative **3,** which proceeded to deprotection of Boc group to get the key intermediate **4** as HCl salt (Scheme **2**).

We then turned our attention towards the synthesis of amide derivatives using precursor **4** gave the corresponding amide derivatives in 75 to 85% of yields. Reactions of different substituted benzoyl chloride with **4**. Initially, the electron-withdrawing group fluorine at *meta* and *para* position gave the products **6a** and **6b** in the yield of 79 and 83%, respectively (Scheme **3**). The *meta* trifluoro substituted compound also gave 79% of product **6c**.

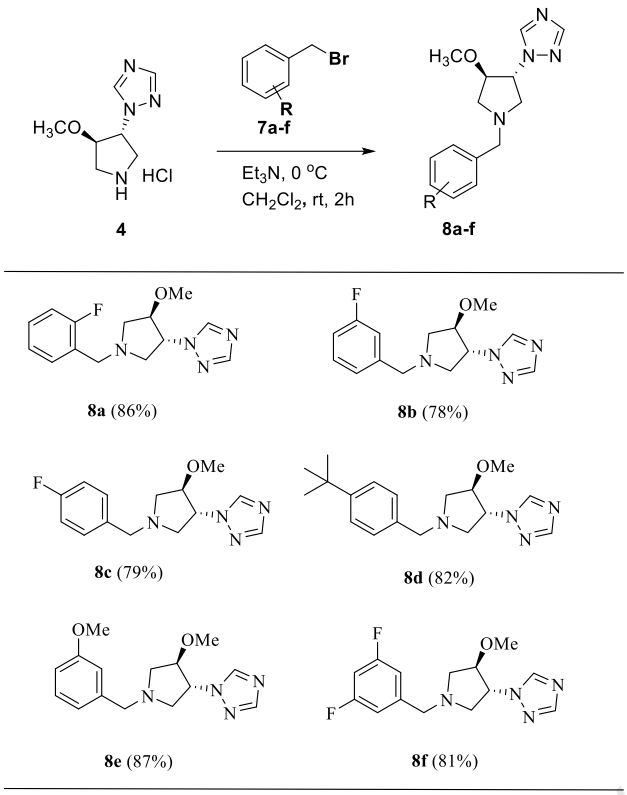


[a] All the reactions were performed by using **4** (0.49 mmol) and **5** (0.54 mmol) using (0.98 mmol) of base in DCM (3 ml).

Scheme 3. Synthesis of amide derivatives (**6a-h**).

Using disubstituted electron-withdrawing groups at *ortho* and *para* positions of **6d** and **6e** gave a yield of 85 and 75%, respectively (Scheme **3**). The disubstituted electron-donating group, *i.e.*, methoxy, gave the product **6f** in 81% yield. The trisubstituted electron-withdrawing group, *i.e.*, fluorine, gave the product **6g** in 81% yield. Furthermore, the disubstituted withdrawing group and electron-donating group such as methoxy, fluorine gave the product **6h** in 79% yield (Scheme-**3**).

In order to expand the substrate scope for the present protocol, we then turned our attention towards the synthesis of amine derivatives using substituted benzyl bromides. The electron-withdrawing group's fluorine at *meta* and *para* position gave the products **8a** and **8b** in the yield of 86 and 78%, respectively (Scheme **4**). Using *para* fluoro substituted also gave the 79% of product **8c**. The electron-donating groups such as tertiary butyl and meta methoxy gave the 82 and 87% yield of product **8d** and **8e,** respectively. The use of disubstituted fluorine gave the 81% of the product **8f** (Scheme **4**). The final products of **6a-h** and **8a-f** were further confirmed by the ^1H and ^{13}C NMR, ESI-MS. (See the Supporting information).



[a] All the reactions were performed using **4** (0.49 mmol) and **7** (0.54 mmol) using (0.98 mmol) of base in DCM (3 ml)

Scheme 4 Synthesis of Benzyl amine derivatives (**8a-f**).

CONCLUSION

In conclusion, a simple and efficient, synthesis of novel urea and amine derivatives such as *trans* 3-methoxy-4-(1H-1,2,4-triazol-1-yl) pyrrolidin-1-yl) (phenyl)methanone (**6a-h**) and *trans* 1-benzyl-4-methoxypyrrolidin-3-yl)-1H-1,2,4-triazole (**8a-f**) were carried out in high yields (75-87%) using *trans*1-(4-methoxypyrrolidin-3-yl)-1H-1,2,4-triazole hydrochloride salt **4** at room temperature.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this study are available from the corresponding author [SA], upon reasonable request.

FUNDING

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CONFLICT OF INTEREST

Shaik Anwar is the Editorial Board Member of the journal, Current Organic Synthesis.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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