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# Base mediated 7-*exo-dig* intramolecular cyclization of Ugi-Propargyl precursors: Highly efficient and regioselective synthetic approach toward diverse 1, 4-benzoxazepine-5(2H)-ones

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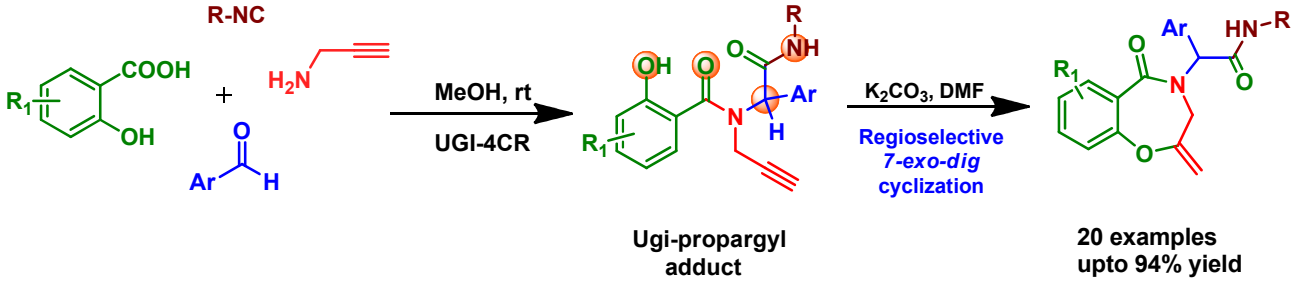

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# Base mediated 7-*exo-dig* intramolecular cyclization of Ugi-Propargyl precursors: Highly efficient and regioselective synthetic approach toward diverse 1, 4-benzoxazepine-5(2H)-ones

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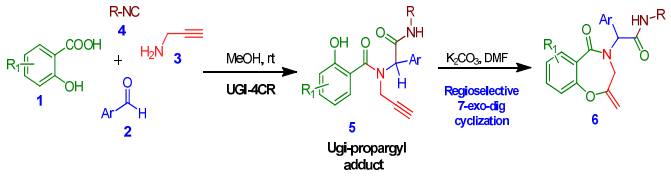
**A metal-free facile and efficient two-step synthetic protocol for the preparation of 1, 4-benzoxazepine-5(2H)-ones derivatives has been developed. The protocol involves Ugi reaction followed by $K_2CO_3$ mediated highly regioselective 7-*exo-dig* intramolecular cyclization of less-nucleophilic oxygen with the pendant alkyne moiety of Ugi-propargyl precursor to afford the 1, 4-benzoxazepine-5(2H)-one derivatives in good to excellent yields.**

Nitrogen-containing heterocycles are well-known for their ubiquitous existence in the realm of natural products, pharmaceuticals and synthetic materials.[1] Amongst these important heterocyclic scaffolds, Benzo-fused seven-membered heterocycles[2] particularly, benzoxazepines are gaining noteworthy attention because of their profound existence in medicinal compounds with remarkable biological and pharmacological activities[3] like anticonvulsant,[4] antidepressant,[5] CNS depressant,[6] antipsychotic[7], neuroleptic,[8] non-nucleoside HIV-1 reverse transcriptase inhibitor[9] and antitumor activity.[10] The fascinating biological profile of this scaffold continues to ensure that they are significant synthetic targets for organic chemists. Accordingly, considerable research efforts have been focused on the development of novel and efficient methods for the synthesis of benzoxazepines.[11] However, the major drawbacks associated with these protocols are the involvement of multistep synthesis, harsh reaction conditions, use of metallic catalyst, poor chemo- and regioselectivities and lack of the diversity within the same molecular framework. Recently, Alper *et al.* reported a new domino aziridine ring-opening/carboxamidation reaction of N-tosylaziridine, carbon monoxide and 2-halophenols for the synthesis of 1,4-benzoxazepine derivatives.[12] More recently, Cai, *et al.* reported the elegant synthesis of 1, 4-benzoxazepine derivatives via the aziridine ring-opening reaction with 2-iodophenol, followed by a palladium catalyzed isocyanide-insertion reaction.[13] Although these protocols represents efficient approaches to expand the structural diversity in single step, however the synthetic potential of these strategies are limited by the use of metal catalyst, toxic carbon monoxide, high cost as well as toxicity of aziridine and stringent reaction conditions. Clearly, there is a need for the development of more versatile and milder route for the synthesis of these compounds.

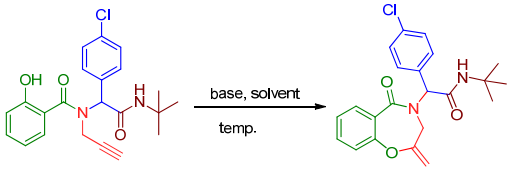
In the recent decades, intramolecular cyclization reaction involving the addition of heteroatom nucleophile to unsaturated carbon–carbon bonds has been extremely exploited for the synthesis of variety of biologically interesting heterocycles via the intramolecular C-O, C-N, C-S bond formation. Indeed, the use of these transformations has effectively provided the access to plethora of five and six membered heterocyclic scaffolds.[14] Nevertheless, scarcely there is any report on the application of this elegant method for the synthesis of seven membered heterocyclic scaffolds which may be due to distal location of the nucleophilic center and the alkyne moiety.[14,15] Additionally, though these reactions are gaining importance because of its efficiency, selectivity as well as mild reaction conditions for cyclization, yet they lack the feature of molecular diversity within the same molecular framework. On the other hand, Ugi reaction followed by its post functionalization is unique reaction sequence which is on front seat for the construction of variety of vastly diverse heterocyclic scaffolds in highly efficient and atom as well as step economical manner as compared to multistep synthesis.[16] Recently, post cycilzation of Ugi-propargyl adduct have been used for the preparation of diverse heterocyclic scaffolds. In this context, Dyker and co-worker have reported the synthesis of isoindoles and dihydroisoquinolines,[17] Van der Eycken and co-worker have reported the elegant synthesis of Spiroindolines, pyrrolopyridinones and pyrroloazepinones, Imidazo[1,4]diazepin-7-ones,[18] Miranda and co-worker have reported the synthesis of 2,3-Dihydropyrroles by taking the advantage of post cyclization of Ugi–alkyne adduct.[19] As a part of our ongoing interest in the development of new strategies for the synthesis of biologically relevant compounds utilizing isocyanide-based multicomponent reactions[20] herein, we report our preliminary results on metal free two step facile, efficient and atom economical protocol for the synthesis of diverse 1, 4-benzoxazepine-5(2H)-ones through 7-*exo-dig* intramolecular cyclization of Ugi-propargyl adduct under basic condition (Scheme-1).

**Scheme-1** Synthetic Approach to 1,4-benzoxazepine-5(2H)-one derivatives.




To the best of our knowledge, there is no report available on the base mediated metal free intramolecular *7-exo-dig* cyclization reaction of less-nucleophilic oxygen with the pendant alkyne moiety of Ugi-propargyl precursor.

**Table-1** Optimization of the reaction conditions for intramolecular cyclization[a]



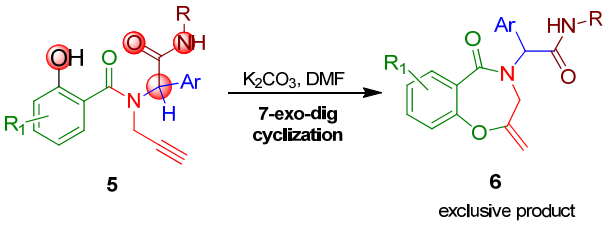

5a 6a

| Entry | Base (mmol) | Solvent | Time(h) | Temp (ºC) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | K$^t$OBu | DMF | 5 | rt | 50 |
| 2 | KOH | DMF | 5 | 55 | 58 |
| 3[c] | $K_2CO_3$ | DMF | 24 | 55 | 72 |
| 4[d] | $Cs_2CO_3$ | DMF | 24 | 55 | 58 |
| 5[e] | $K_3PO_4$ | DMF | 24 | 55 | 64 |
| 6[f] | $K_2CO_3$ | DMF | 24 | 55 | 74 |
| **7** | **$K_2CO_3$** | **DMF** | **2** | **90** | **92** |
| 8 | $K_2CO_3$ | DMSO | 2 | 90 | 90 |
| 9 | $K_2CO_3$ | ACN | 3.5 | 80 | 85 |
| 10 | $K_2CO_3$ | THF | 4 | 65 | 65 |
| 11 | $K_2CO_3$ | MeOH | 3 | 60 | 88 |
| 12 | $K_2CO_3$ | Toluene | 6.5 | 90 | 74 |
| 13 | $K_2CO_3$ | Dioxane | 5 | 90 | 78 |

[a] Reaction conditions: **5a** (0.50 mmol), base(1.0 mmol), solvent (2.5 mL). [b]Isolated yield. [c]14 % **5a** was recovered. [d] 26 % **5a** was recovered. [e]22 % **5a** was recovered yield. [f]1.5 mmol $K_2CO_3$ was used

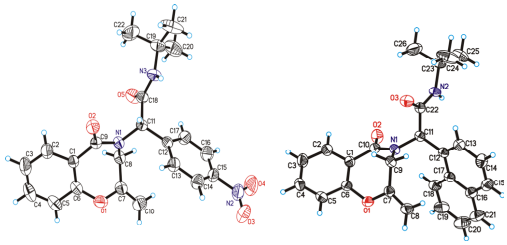
To study the intramolecular cyclization, a series of Ugi-propargyl adduct were used as precursors, which were easily prepared by Ugi-4CR using various aldehydes, propargylamine as the amine input, 2-hydroxybenzoic acid as acid input, and isocyanides. The investigation commenced with the screening of reaction conditions for bases, solvents and reaction temperature using Ugi-propargyl adduct 5a as the model substrate (Table 1). Among the various protocols reported in literature for intramolecular cyclization, we planned to initiate with base mediated cyclization. Initially, the reaction was carried out with substrate 5a with 2 equiv. of K$^t$OBu in DMF at rt for 5h, the reaction was very sluggish and furnished a mixture of products with the formation of 6a in 50% isolated yield (Table 1, entry 1). Presumably, the activation of all the four potential nucleophilic sites, i.e. the phenolic OH, the α-C of the secondary amide, the oxygen and NH of the secondary amide for intramolecular cyclization might be the reason of moderate yield. Consequently, we carried out reaction in the presence of mild bases as $K_2CO_3$, $Cs_2CO_3$, $K_3PO_4$ (entries 3-5). Interestingly, in all cases 6a was obtained as the sole isomer with rest of starting recovered. Among all the bases screened, best result was obtained with $K_2CO_3$, provided the product in moderate yield (entry 3). Next, in order to progress the reaction to completion, we carried out reaction at higher temperature of 90 ºC. Pleasingly the reaction proceeded smoothly with the complete consumption of starting material and formation of desired product exclusively in excellent yield (entry 7). Next, different solvents were screened with 2 equiv $K_2CO_3$ as base. Nevertheless, no obvious improvement in the yield was observed when the solvent was switched to DMSO, ACN, MeOH, THF, toluene and 1, 4-dioxane (entries 8–13). It is interesting to mention that despite the presence of four potential nucleophilic centers in Ugi –propargyl adduct, the reaction was completely regioselective and provided only one regioisomer **6** via intramolecular *7-exo-dig*-cyclization involving phenolic-OH as nucleophile (Scheme-2).

**Scheme-2** Regioselective formation of diverse benzoxazepinones through 7-exo-dig intramolecular cyclization of phenolic-OH on pendant Ugi-propargyl adduct




With the optimized reaction condition established above for the synthesis of 6a, we turned our attention to study the scope of the intramolecular *7-exo-dig* cyclization reaction to construct 1, 4 benzodiazepine-5-one derivatives. The reaction appears to be versatile, and 20 compounds **6(a−t)** were synthesized in 76−94% yield.

**Figure-1.** ORTEP diagrams drawn with 30% ellipsoid probability for non-H atoms of the crystal structure of compounds **6d** and **6i** determined at 293 K.

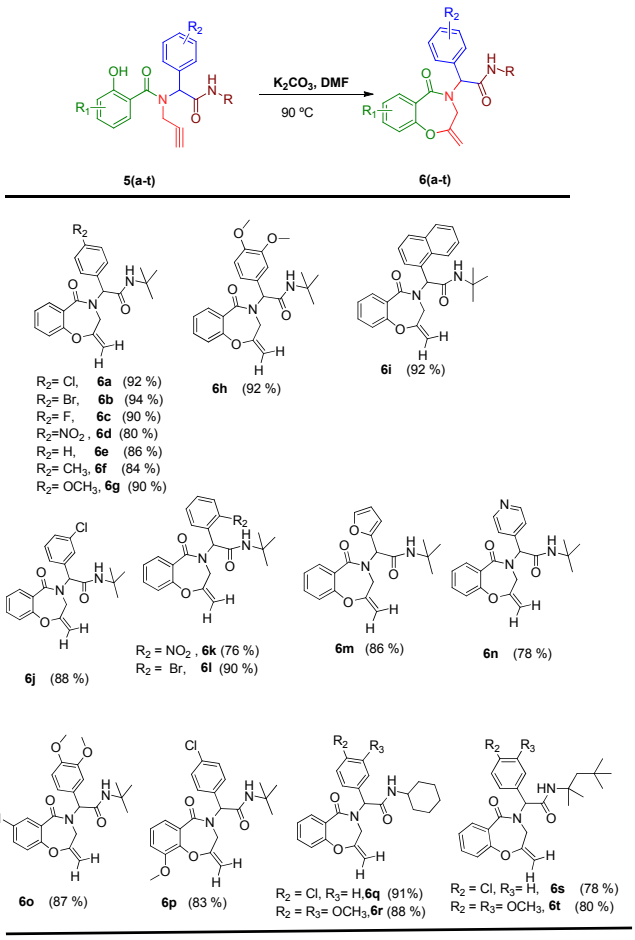


6d 6i

The structure of the products **6(a−t)** were deduced from their IR, HRMS, $^1$H NMR, and $^{13}$C NMR spectra. Furthermore, the structure of compounds 6d and 6i were unambiguously assigned by X-ray crystallography (Figure 1). Gratifyingly, aromatic aldehyde with either electron withdrawing **(6a-d)** or electron donating **(6f-h)** groups on the benzene ring could be smoothly transformed into the desired products in good to excellent yields (Table 2). Furthermore, the presence of substituents at the ortho-, meta- and para- positions also had no noticeable effect on the yields of the desired product and all the products were obtained in high yields. It is noteworthy that Ugi adduct with heteroaromatic aldehydes such as pyridine-4-

carboxaldehyde and furan-2-carboxaldehyde were also compatible with the reaction conditions and generated the corresponding product **(6m-n)** in high yields.

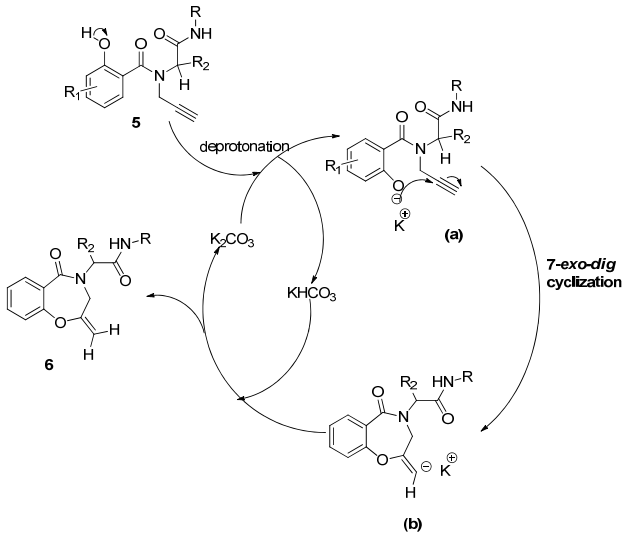
**Table-2** Scope of the intramolecular cyclization reaction[a]




The effect of substituents on the 2-hydroxy benzoic acid was also studied. As shown in Table 2, the reactions employing 2-hydroxy benzoic acid bearing 5-chloro and 3-methoxy, groups also worked well to furnish the corresponding 1, 4-benzoxazepine-5(2H)-ones. Next, different isocyanides were also applied to probe the scope of the reaction. In case of isocyanides, tert-butyl and cyclohexyl isocyanides both provided the product in excellent yields. The Ugi precursor containing 1, 1, 3, 3-tetramethylbutyl as R group also underwent cyclization smoothly to afford the corresponding product (6s-t) in albeit low yield.

On the basis of the results presented above, we postulated the following possible mechanism for the formation of these 1, 4-benzoxazepine-5(2H)-one derivatives (Scheme 3). Abstraction of an acidic proton by potassium carbonate results in generation of phenolate ion (a). The anion thus formed undergoes *7-exo-dig* intramolecular cyclization reaction with the pendant alkyne group to give intermediate (b). Subsequent protonation of (b) by the conjugate acid $KHCO_3$, leads to the formation of desired 1,4-benzoxazepine-5(2H)-one derivatives.

**Scheme-3.** Possible mechanism for *7-exo-dig* cyclization reaction of Ugi-propargyl adduct-5




## Conclusions

In summary, we have successfully developed a novel and efficient synthetic strategy to construct structurally diverse 1, 4-benzoxazepine-5(2H)-one derivatives via Ugi-4CR followed by base mediated 7-*exo-dig* intramolecular cyclization. The protocol was successful with the broad range of commercially available 2-hydroxy benzoic acids, aromatic aldehydes, and isocyanides affording the desired products in high to excellent yields The strategy allows synthesis of biologically important molecules in highly regioselective, straightforward and atom-economical fashion, therefore provides an opportunity for the rapid generation of a library of highly diverse 1,4-benzoxazepine-5(2H)-one derivatives for combinatorial and medicinal chemistry.

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## Notes and references

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Electronic Supplementary Information (ESI) available: [Experimental procedures, spectroscopic data, and copies of $^{1}H$ and $^{13}C$ NMR spectra for all compounds are provided]. See DOI: 10.1039/c000000x/

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