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ARTICLE TYPE

Copper catalysed [3+2] cycloaddition with concomitant annulation: Formation of 2,4-diaryl-1,4-oxazepan-7-ones *via* ketenimine route

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A novel strategy of copper catalyzed cascade reaction involving intramolecular nucleophilic addition to *N*-sulfonylketenimine gratifyingly furnishing 1,4-diaryl oxazepan-7-one has been described.

Introduction

Heterocycles act as synthons for potent pharmaceutical drugs and posses various biological activities. 1,4-Oxazepane derivatives represent an extensive group of crucial heterocyclic compounds, several of which find applications as dopamine D_4 receptor ligands,[1] fungal EF-2 inhibitors,[2] telomerase inhibitors,[3] glycosidase inhibitors,[4] inhibitors of nitric oxide synthases[5] and human A_{2A} receptor antagonists.[6] They also exhibit anti-fungal, antibacterial[7] and anticonvulsant[8] activities. The basic unit oxazepane is found in important natural products such as neurotoxin and batrachotoxin (Figure 1).[9] These factors ensure that 1,4-oxazepane derivatives are important synthetic targets for organic chemists.[10] Popular methods available for the synthesis of 1,4-oxazepane derivatives includes reductive etherification,[11] reductive amination,[12] phosphine-triggered tandem [3+4] annulation reaction[13] S_N2-type ring opening reaction,[14] Solid-Phase Synthesis,[15] Liquid-Phase Synthesis,[16] Cu(I)-catalyzed cycloaddition reaction[17] and several multistep reactions.[18]

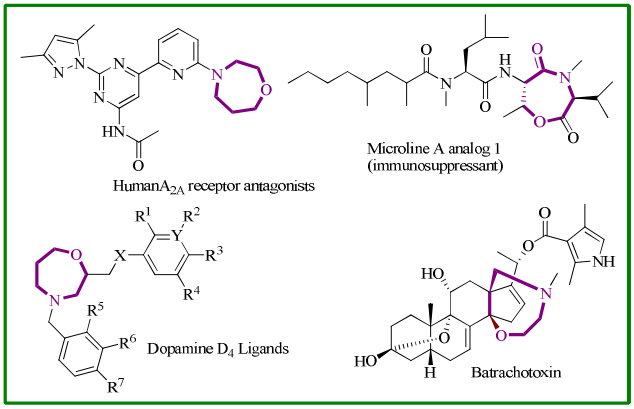
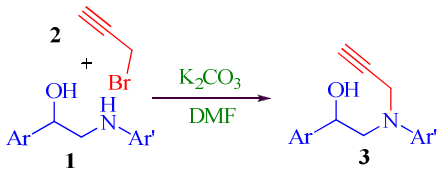


Fig 1. Some bioactive 1,4-oxazepanes

Ketenimines are nitrogenated heterocumulenes that have attracted considerable interest due to their easy access and high reactivity getting themselves recognized as excellent precursors. The most attractive and sustainable method for the construction of ketenimines could be the copper catalyzed azide-alkyne cycloaddition reaction because of its mild reaction conditions.[19] The ketenimines produced by the above protocol can be subjected to nucleophilic attack by amines, alcohols or water leading to amidines, imidates and amides respectively. It has been shown that substrates containing both a triple bond and a nucleophile, when added with sulfonyl azide, yield cyclic compounds.[20] This phenomenon has been explored and applied in the assembly of various heterocycles.

Results and discussion

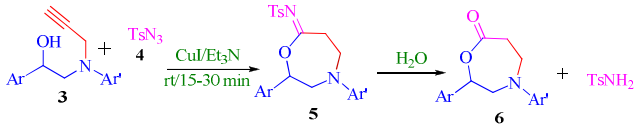
In continuation of our studies aiming at the development of efficient strategies for accessing privileged heterocycles from open chain compounds,[21] it has been planned to make use of the reactivity of ketenimine functionality to generate new heterocyclic compounds. In this attempt, a seven membered ring, 2,4-diaryl-1,4-oxazepan-7-one nucleus, has been generated by an efficient one-pot procedure from easily available starting materials under mild conditions. An interesting cascade process, a nucleophilic addition followed by hydrolysis, has been observed during this reaction. Thus the journey for the new class of 2,4-diaryl-1,4-oxazepan-7-one derivatives started from the synthesis of 1-aryl-2-(phenyl(prop-2-ynyl)amino)ethanol **3** (Scheme 1), which was obtained by the reaction of reduced monophenacyl anilines **1** and propargyl bromide **2**.



Scheme 1. Synthesis of 1-aryl-2-(aryl(prop-2-ynyl)amino)ethanol **3**

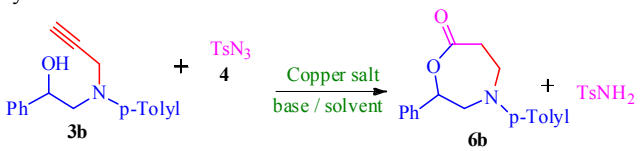
The structure of the alkynes **3** was established from ^1H, ^{13}C and two dimensional NMR spectral data.

Ketenimines are known to react with nucleophiles yielding amidines. Accordingly, we examined the reaction of alkyne **3** with tolylsulfonyl azide **4** in the presence of copper iodide and triethylamine in dichloromethane at room temperature (Scheme 2). Instead of the anticipated *N*-(2,4-diphenyl-1,4-oxazepan-5-ylidene)-4-methylbenzenesulfonamide **5** (Scheme 2), 2,4-diphenyl-1,4-oxazepan-7-one **6** was obtained in good yield.



Scheme 2. Synthesis of 2,4-diaryl-1,4-oxazepan-7-one derivatives **6**

Table 1. Optimization of solvents and bases towards the synthesis of **6b**

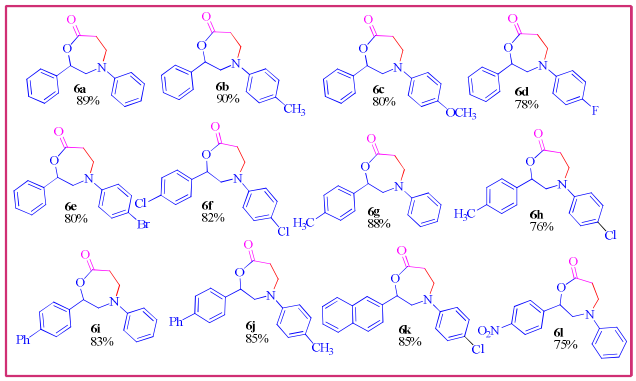


Entry	Catalyst	Base	Solvent	Yield (%)	Reaction time (h)
1	CuI (20 mol %)	TEA	DCM	90	0.5
2	CuI (10 mol %)	TEA	DCM	90	0.5
3	CuI (5 mol %)	TEA	DCM	85	3.0
4	CuBr (10 mol %)	TEA	DCM	83	0.5
5	CuCl (10 mol %)	TEA	DCM	65	0.5
6	CuI (10 mol %)	K_2CO_3	DCM	57	5.0
7	CuI (10 mol %)	Pyridine	DCM	42	5.0
8	CuI (10 mol %)	TEA	DCE	70	1.0
9	CuI (10 mol %)	TEA	THF	68	1.5
10	CuI (10 mol %)	TEA	CH_3CN	44	6.0
11	CuI (10 mol %)	TEA	Toluene	42	6.0

The optimized reaction conditions for the formation of **6b** were summarized in Table 1. Among the several solvents and catalysts tested, dichloromethane in combination with copper (I) iodide appeared to be superior than the others. The desired product could be obtained in 42−90% yield using CH_3CN, THF, DCE, toluene and CH_2Cl_2 as solvents. Dichloromethane has been found to be the solvent of choice. Other bases like pyridine and potassium carbonate resulted in lower yield of **6b**. It has been found that the presence of copper catalyst in less than 10 mol % yielded the product quantitatively but required more time for the completion of the reaction (Table 1, entries 2 and 3). Addition of the catalyst in higher mole ratio has also not resulted in any improvement (Table 1, entry 1).

Sulfonyl azides with tosyl, mesyl and naphthyl groups also reacted well to give the respective **6** in excellent yields. Respective amines were isolated and identified in some cases. Differently substituted 1,4-oxazepane derivatives were obtained by employing differently substituted phenacyl bromides and anilines (Table 2). It is pertinent to note that in a related reaction, an interesting rearrangement has been observed.[21b]

Table 2. Synthesis of 2,4-diaryl-1,4-oxazepan-7-one derivatives **6** [a]



[a] Reaction Conditions: *p*-Toluenesulfonyl azide (1.2 mmol), 3 (1.0 mmol), TEA (2.0 mmol), copper (I) salt, solvent (10 mL), rt

The structure of the oxazepanes was established from ^1H, ^{13}C and two dimensional NMR spectral data as illustrated for a representative example **6d** (Figure 2).

A plausible mechanism for the copper catalyzed intramolecular cyclization of electron deficient alkynes **2** is illustrated in Scheme 3. The reaction is believed to proceed initially through the ketenimine intermediate, generated by the addition of copper acetylide to sulfonyl azide, which is trapped by the nucleophilic centre present in the same compound. The intramolecular nucleophilic attack on the ketenimine central carbon results in the intramolecular ring closure followed by hydrolysis to the 2,4-diaryl-1,4-oxazepan-7-one (Scheme 3).

The possibility of initial propargylation at oxygen followed by cylisation can also be thought of. In that case, the final product is a seven membered lactam and not a lactone. However the HMBC connections and the fact that the IR spectrum **6e** has a band at 1718 cm^{-1} clearly indicate that the compound formed is a lactone and not a lactum.

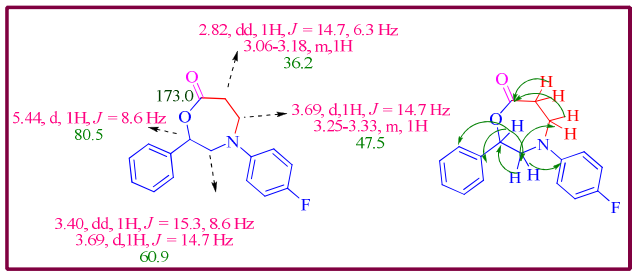
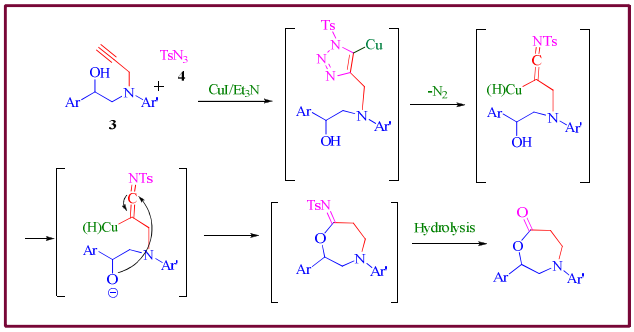


Fig. 2. ^1H and ^{13}C NMR assignments & selected HMB correlations of compound **6d**



Scheme 3. Plausible mechanism for the synthesis of 2,4-diaryl-1,4-oxazepan-7-one **6**

Conclusions

A copper-catalyzed cascade reaction involving intramolecular nucleophilic addition to *N*-sulfonylketenimine furnishing cyclic sulfonimidate, which subsequently undergoes hydrolysis, has been described. A seven membered ring, 2,4-diaryl-1,4-oxazepan-7-one nucleus, has been successfully constructed. The present method may be considered as a simple route for the synthesis of substituted 1,4-oxazepan-7-ones due to the short reaction time and readily available starting materials and catalyst.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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Graphical abstract

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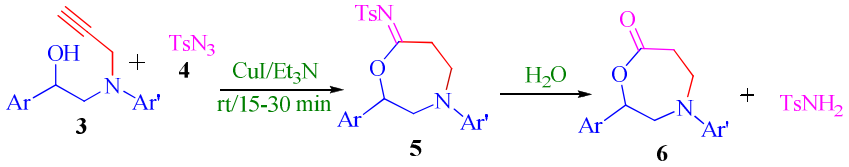

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