An expedient approach to substituted triazolo[1,5-a][1,4]benzodiazepines via Cu-catalyzed tandem Ullmann C-N coupling/ azide-alkyne cycloaddition

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An expedient approach to substituted triazolo[1,5-*a*][1,4]benzodiazepines *via* Cu-catalyzed tandem Ullmann C-N coupling/ azide-alkyne cycloaddition

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Abstract: An approach to the synthesis of triazolo[1,5-*a*][1,4]benzodiazepines comprising copper catalyzed tandem Ullmann C–N coupling followed by azide-alkyne cycloaddition has been described. The reaction of *o*-azidobenzylbromide and N-propargylated aniline derivatives in presence of CuI and base leads to the formation of triazolo[1,5-*a*][1,4]benzodiazepines. The reaction has been successfully generalized by synthesizing a number of triazolo[1,5-*a*][1,4]benzodiazepine derivatives in good to excellent yields.

Key-words: Fused triazoles; 1,4-Benzodiazepine; Azide-alkyne cycloaddition; Ullmann C–N coupling; CuI; *o*-azido-benzylbromide, *N*-propargylated aniline

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Benzodiazepines are known to provide ligands for many bio-receptors and widely used as the privileged structures in medicinal chemistry[1]. Among them, 1,4-benzodiazepines are the most important class of therapeutic agents with widespread biological activities[2] including anti-anxiety, anticonvulsant, tranquilizing, sedative effects[3] and also act as antihistaminic agents[4]. Moreover, these therapeutic activities have been significantly enhanced through the fusion of the 1,4-benzodiazepine moiety with a triazole ring[5]. Several benzodiazepines fused with a triazole ring are known to possess potent biological activity[6]. Diazepine[7] (**1**) and estazolam[8] (**2**) have achieved clinical success in the treatment of CNS disorders. Again, alprazolam (**3**) and estazolam (**2**) are used as anxiolytic agents[9], whereas triazolam (**4**) and adinazolam (**5**) are known as antidepressants[10] (Figure 1).

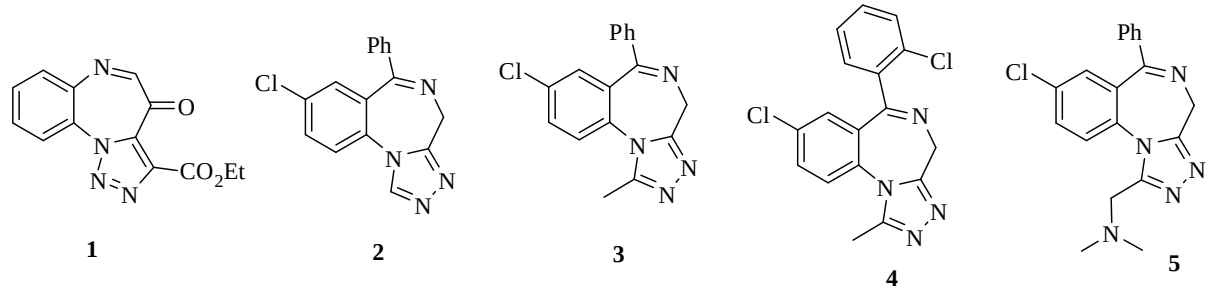
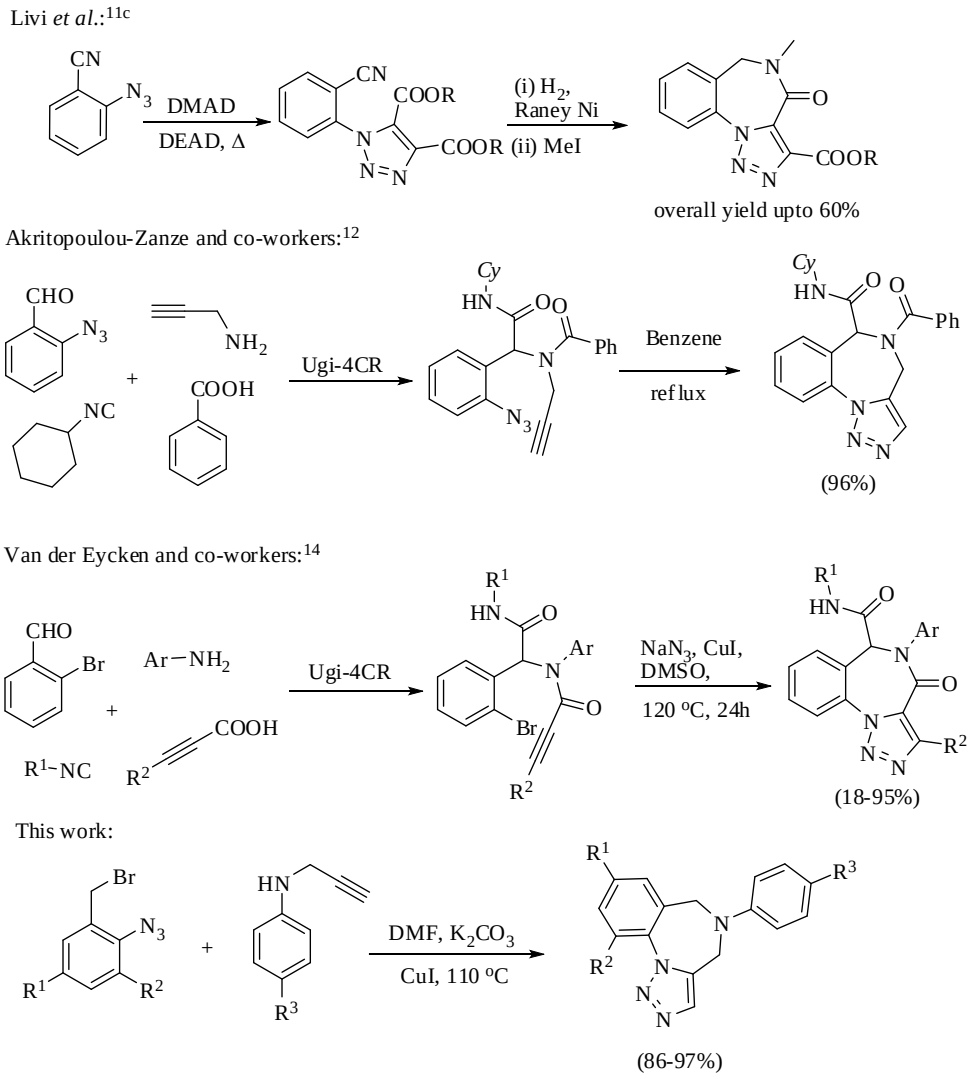


Figure 1: Some biologically active fused benzodiazepines

Various approaches have been reported[11] to synthesize triazole-fused 1,4-benzodiazepine derivatives (Scheme 1). Akritopoulou-Zanze *et al.* reported[12] a two-step synthesis of fused triazolo derivatives using alkyne-azide cycloaddition reaction from the Ugi-product that required isocyanide and *o*-azido benzaldehyde. Hemming and co-workers have reported[13] the synthesis of triazolobenzodiazepines and pyrrolobenzodiazepines using intramolecular 1,3-dipolar cycloaddition reaction in a multistep process. Very recently, Van der Eycken *et al* the synthesis of triazolo[1,5-*a*][1,4]benzodiazepinones by employing a post-Ugi Cu-catalyzed tandem azide-

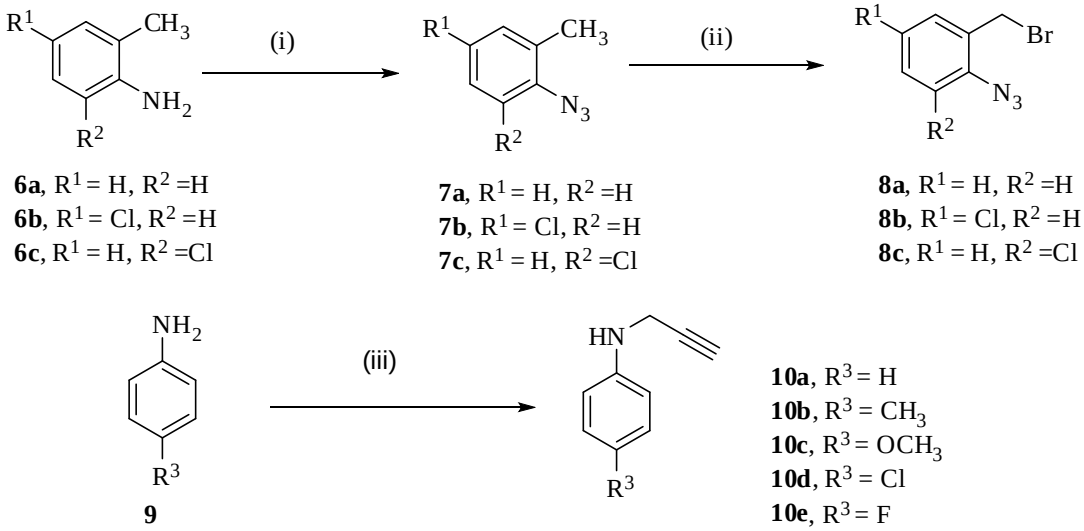
alkyne cycloaddition/Ullmann coupling strategy. They used *o*-bromobenzaldehyde, amine, isocyanide, and propiolic acid derivatives for the preparation of Ugi-product.



Scheme 1: Different approaches towards triazolo-fused [1,4]benzodiazepine derivatives

Development of mild and simple method to synthesize triazole-fused 1,4-benzodiazepines is still desirable because of their biological significance. As part of our continuing efforts to synthesize potentially bioactive heterocycles[15] we have planned to develop a new protocol for synthesizing triazolo[1,5-*a*][1,4]benzodiazepine by copper-catalyzed tandem Ullmann C-N coupling followed by azide-alkyne cycloaddition reaction[16]. Herein we report our results.

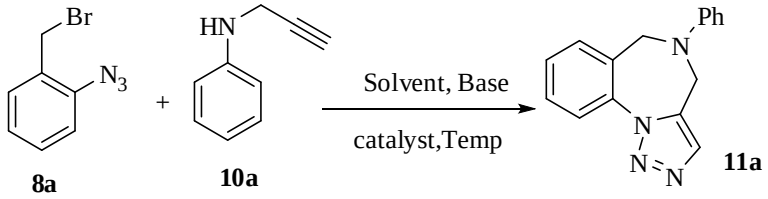
At first *o*-toluidines (**6a-c**) were converted into their azide derivatives (**7a-c**) using diazotization condition. Necessary precursors **8a-c** were prepared in good yields from the reaction[17] of *o*-azidotoluene (**7a-c**) with *N*-bromosuccinimide and benzoyl peroxide in refluxing dry benzene. On the other hand, *N*-propargylated anilines (**10a-e**) were prepared by the reaction of aniline **9** with propargyl bromides in the presence of anhydrous potassium carbonate in DMF for five hours (Scheme 1).



Scheme 1 *Reagent and conditions:* (i) $NaNO_2$, 6(N) HCl, NaN_3 (ii) NBS, benzoyl peroxide, benzene, reflux, 4.5h (iii) propargyl bromide, DMF, K_2CO_3, r.t, 5h

We initiated our study by the reaction of *o*-azidobenzylbromide (**8a**) and *N*-propargylated aniline **10a** at room temperature using DMF as solvent, K_2CO_3 as base and CuI as a catalyst. But this reaction did not give any cyclized product (entry 1, Table 1).

Table 1. Tandem Ullmann C-N coupling/azide-alkyne cycloaddition using various conditions[a]



8a **10a** **11a**

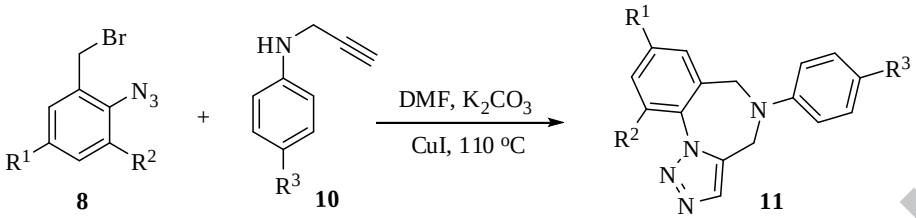
Entry	Solvent	Base	Catalyst	Temp (^oC)	Time (h)	Yield (%)[b]
1	DMF	K_2CO_3	CuI	r.t.	12	0
2	**DMF**	**K_2CO_3**	**CuI**	**110 ^oC**	**5**	**92**
3	DMSO	K_2CO_3	CuI	110 ^oC	7	74
4	Toluene	K_2CO_3	CuI	110 ^oC	7	0
5	1,4-dioxane	K_2CO_3	CuI	reflux	7	0
6	DMF	Cs_2CO_3	CuI	110 ^oC	5	85
7	DMF	Et_3N	CuI	110 ^oC	5	77
8	DMF	Na_2CO_3	CuI	110 ^oC	5	<50
9[c]	DMF	_	CuI	110 ^oC	12	0
10	DMF	K_2CO_3	CuCl	110 ^oC	5	43
11	DMF	K_2CO_3	CuBr	110 ^oC	5	50
12	DMF	K_2CO_3	$CuSO_4$	110 ^oC	5	67
13[d]	DMF	K_2CO_3	CuI	110 ^oC	5	89
14[e]	DMF	K_2CO_3	_	110 ^oC	12	0
15[f]	DMF	K_2CO_3	CuI	110 ^oC	5	87

All the reactions were carried out using 1 equiv **8a** and 1 equiv **10a** and 1.5 equiv base and 10 mol% catalyst [*b*] isolated yields [*c*] no base was used [*d*] 20 mol% CuI was used as catalyst [*e*] reaction was carried out without any catalyst [*f*] 20 mol % L-proline was used as ligand with 10 mol% CuI

Application of heat at 110 ^{o}C to this reaction gave satisfactory result affording the desired product in 92% yield within 5h (entry 2, table 1). We have conducted the same reaction in other solvents like DMSO, toluene, 1,4-dioxane, but none of them could improve the yield of the product (entry 3-5, Table 1). The use of DMF as solvent gives the desired product in highest yield. Then we carried out some reaction by replacing the base K_2CO_3 with other bases like Cs_2CO_3, Et_3N or Na_2CO_3 but no improvement of the yield of cyclized product was observed (entry 6-8, Table 1). The reaction did not occur at all in the absence of any base (entry 9, Table 1). To investigate the role of catalyst used we set up some reaction using different Cu-sources. Use of CuCl, CuBr as catalyst gave 43% and 50% yield of the cyclized product (entry 10, 11, Table 1), whereas the use of $CuSO_4$ as the Cu-source afforded 67% yield of the product (entry 12, Table 1). Further catalyst loading (20 mol % CuI) did not improve the yield of the cyclized product (entry 13, Table 1). The reaction without any catalyst did not give any cyclized product at all (entry 14, Table 1). Again no significant change in the yield was observed by adding L-proline as a ligand (entry 15, Table 1).

From the above set of experiments, the optimized condition developed is to treat 1 equiv. of *o*-azidobenzylbromide with 1 equiv. *N*-propargylated aniline, 1.5 equiv. K_2CO_3, 10 mol% CuI in DMF at 110 ^{o}C for 5-6h. To generalize this reaction we have synthesized various triazolo[1,5-*a*][1,4]benzodiazepines (**11a-i**) and the results are summarized in Table 2.

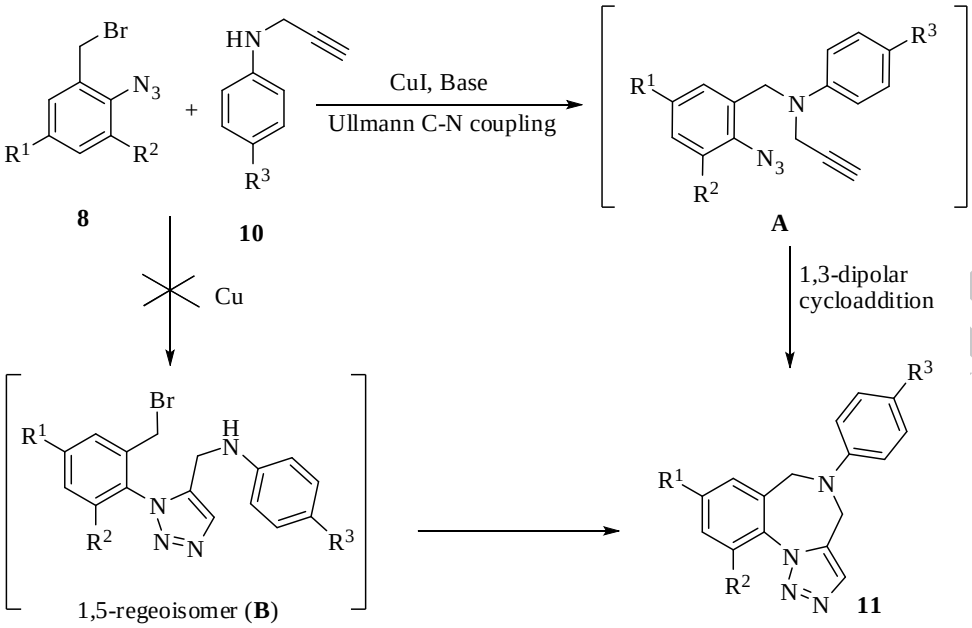
Table 2: Cu-catalyzed tandem Ullmann C–N coupling/ azide-alkyne cycloaddition reactions with various substrates[a]



Entry	Azide	Amine	Time (h)	Product	Yield[b] (%)
1	**8a**, R^1 = H, R^2 = H	**10a**, R^3 = H	5	**11a**, R^1 = H, R^2 = H, R^3 = H	92
2	**8a**, R^1 = H, R^2 = H	**10b**, R^3 = Me	6	**11b**, R^1 = H, R^2 = H, R^3 = Me	95
3	**8a**, R^1 = H, R^2 = H	**10c**, R^3 = OMe	6	**11c**, R^1 = H, R^2 = H, R^3 = OMe	91
4	**8a**, R^1 = H, R^2 = H	**10d**, R^3 = Cl	5	**11d**, R^1 = H, R^2 = H, R^3 = Cl	88
5	**8a**, R^1 = H, R^2 = H	**10e**, R^3 = F	5	**11e**, R^1 = H, R^2 = H, R^3 = F	86
6	**8b**, R^1 = Cl, R^2 = H	**10a**, R^3 = H	5	**11f**, R^1 = Cl, R^2 = H, R^3 = H	90
7	**8b**, R^1 = Cl, R^2 = H	**10b**, R^3 = Me	6	**11g**, R^1 = Cl, R^2 = H, R^3 = Me	89
8	**8b**, R^1 = Cl, R^2 = H	**10e**, R^3 = F	5	**11h**, R^1 = Cl, R^2 = H, R^3 = F	85
9	**8c**, R^1 = H, R^2 = Cl	**10a**, R^3 = H	6	**11i**, R^1 = H, R^2 = Cl, R^3 = H	82

[*a*] *Reaction conditions*: compound **8** (1 equiv.), propargylated aniline **10** (1 equiv.), K_2CO_3 (1.5 equiv.), 10 mol% CuI were heated at 110 ^oC in DMF, [*b*] isolated yields of **11**

According to the literature, we know that copper-catalyzed cycloaddition reaction affords exclusively the 1,4-regioisomers[18] and initial formation of the intermediate **B** is not possible using Cu-catalyst. Hence the reaction can go through the initial formation of intermediate **A** *via* Cu-catalyzed intermolecular C-N coupling of compound **8** with amine **10**. Intermediate **A** may undergo intramolecular azide-alkyne cycloaddition yielding the triazole-fused benzodiazepines **11** (Scheme 2).



Scheme 2: Rationalization for the formation of compound **11**

Most of the earlier protocols for the synthesis of triazole-fused benzodiazepines- [-11c, -12, -14] used costly reagents and sometime occurs in a multistep manner, while our method is straightforward, uses inexpensive reagent and is devoid of any ligand. In conclusion, we have developed a simple approach for the synthesis of triazolo[1,5-*a*][1,4]benzodiazepines derivatives with potential biological activity through the combination of C-N coupling reaction and intramoleculer 1,3-dipolar cycloaddition reaction in a tandem fashion. This ligand-free protocol provides advantages in terms of excellent yield, step-economy, ease of operation and substrate scope.

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Graphical Abstract

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