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A One-Pot Synthesis of Triazolodiazepines

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A one-pot sequential A^3-coupling-azidation-cyclisation approach leading to potentially biologically active diazepine analogues has been developed. The implementation of the A^3-coupling reaction ensures diversity. Attention is given to this so far rarely studied structural motif of fused heterocyclic diazepines.

Introduction

The 1,4-benzodiazepine motif is an integral part of many drugs,[1] therapeutic leads[2] and naturally occurring bioactive substances.[3] It is the archetypical example of a privileged structure as coined by Evans et al. in 1988.[4] Compounds possessing the 1,4-benzodiazepine scaffold show a broad range of biological activities[5] and can bind to a multitude of targets, such as ligand-gated ion channels, enzymes, and G-protein-coupled receptors.[6] Modifications of the benzodiazepine scaffold are well documented in the literature; a frequent applied strategy is fusing the benzodiazepine motif with a heterocyclic moiety in order to tune the activity.[7] The most notable examples of the fusion with a triazole moiety are alprazolam, estazolam, triazolam and adinazolam. The former two are used as anxialotic agents,[8] whereas the latter ones are known as antidepressants.[9] Recently, several reports on the synthesis of triazolo-fused benzodiazepines have been published.[10] Given the structural resemblance it is surprising that only few studies can be found on the syntheses and biological activity of triazolo-fused diazepines, which are not fused with a (hetero)-aromatic ring (Scheme 1).[11] Lamaty and co-workers described the synthesis of *trans*-disubstituted triazolodiazepines **2** originating from linear azidoalkynes **1**, which derive from protected β-amino esters. This thermal Huisgen cycloaddition step is shown in Scheme 1a.[11a] In Scheme 1b the sequential approach of Pericas and co-workers is presented. It consists of the opening of an epoxide **3** with NaN_3 followed by a thermal Huisgen cycloaddition.[11b] Ballet and co-workers published two synthetic sequences towards triazolodiazepinones as analogues of conformationally restrained amino acids **6**, starting from azido esters and propargylamine, which can be seen in Scheme 1c.[11c] Recently, they published a one-pot protocol based upon an Ugi four-component reaction starting from azido amino acid **8**, presented in Scheme 1d.[11e] However, these existing synthetic methods are based on multistep sequences, which limit the possibility for easily generating small libraries of diversely substituted triazolodiazepines.

In this work we present a one-pot sequence for the synthesis of 5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-*a*]diazepines. This process is based on a tandem A^3-coupling[12]-azidation-cyclisation reaction, employing readily available starting materials. The implementation of the A^3-coupling as multicomponent reaction ensures the generation of diversity. The required *N*-substituted 3-chloropropylamines are easily generated from 3-chloropropylamine hydrochloride by reductive amination. The retrosynthetic analysis is shown in Scheme 2.

Results and Discussion

Based on our knowledge from previous works on A^3-coupling reactions[13] we optimized the individual steps separately from the one-pot reaction, which is shown in Scheme 3. In Table 1, Entry 1 we used 1.5 equiv. of phenylacetylene;[13b] however, in order to avoid possible side reactions in the one-pot sequence, we reduced the amount of phenylacetylene in Entries 2–8 of Table 1. With CuBr as catalyst the reaction gave good yields under both microwave and conventional heating, which can be seen in Table 1, Entries 1–2 and 3–4, respectively. Reducing the catalyst loading in Table 1, Entry 4 to 5 mol-% resulted in a lower yield. Using DMSO or DMF in Table 1 in Entries 5–8 as solvent resulted in significantly lower yields. However, in Entries 9 and 10 of Table 1 both EtOH and acetonitrile (ACN) performed well, and good yields were obtained.

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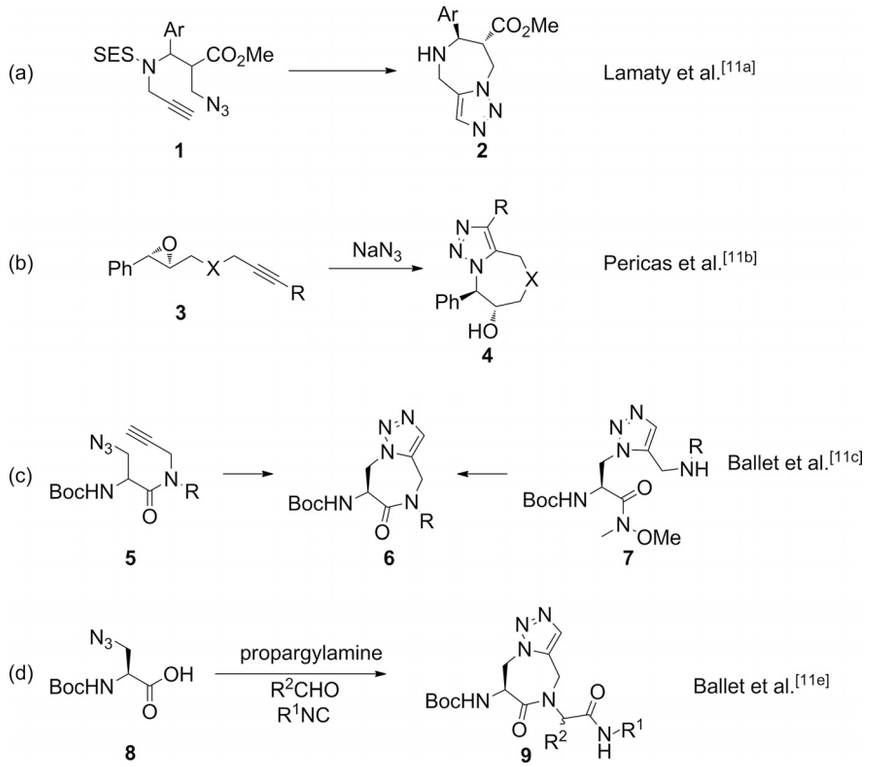
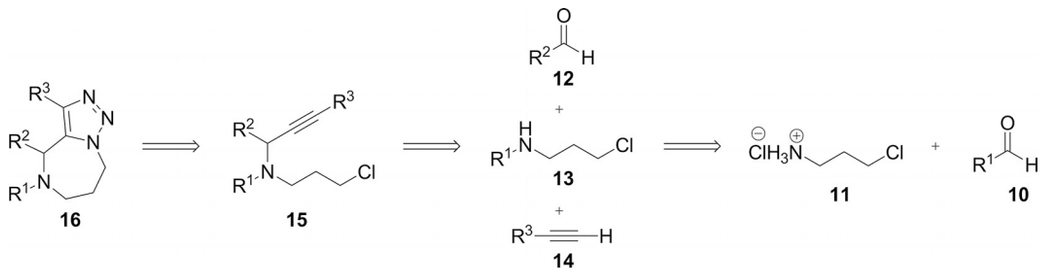
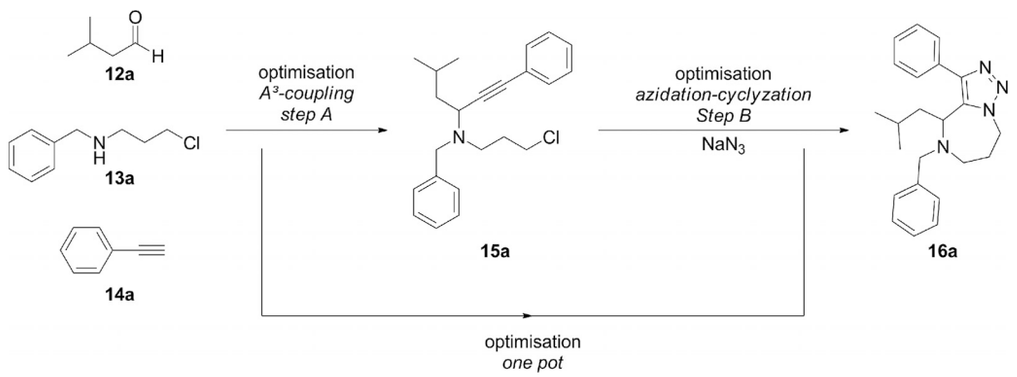


Scheme 1. Literature procedures to triazolo-fused diazepines.



Scheme 2. Retrosynthetic analysis.



Scheme 3. Optimisation of the reaction conditions.

Subsequently, we focused on optimising the azidation-cyclisation sequence. In Table 2, Entry 1 we started the optimisation by running the reaction with NaN_3 in DMSO at 120 °C for 16 h. Adding 15-crown-5 slightly improved the yield of the reaction as shown in Table 2 in Entries 2–7. Extending the reaction time to 24 h further improved the

Table 1. Optimisation of the A^3-coupling reaction conditions.[a]

Entry	Equiv 12a	Catalyst (mol-%)	Solvent	Temp. [°C]	Time	Yield [%][b]
1	***1.5***	***CuBr (10)***	***toluene***	***100***	***45 min***[c]	***81***
2	0.9	CuBr (10)	toluene	100	45 min[c]	78
3	***0.9***	***CuBr (10)***	***toluene***	***100***	***3 h***	***81***
4	0.9	CuBr (5)	toluene	100	3 h	62
5	0.9	CuBr (10)	DMSO	100	45 min[c]	40
6	0.9	CuBr (10)	DMSO	100	3 h	35
7	0.9	CuBr (10)	DMF	100	45 min[c]	42
8	0.9	CuBr (10)	DMF	100	3 h	39
9	0.9	CuBr (10)	EtOH	100	45 min[c]	75
10	0.9	CuBr (10)	ACN	100	45 min[c]	72

[a] Reaction conditions: **13a** (1 mmol, 1 equiv.) and 3-methylbutyraldehyde (**12a**) (1.3 mmol, 1.3 equiv.) in the indicated solvent (0.5 mL). [b] Isolated yields. [c] The reaction was run under microwave irradiation at 80 W maximum power.

yield to 60% in Entry 3 of Table 2. In order to optimize a one-pot reaction in Table 2, Entries 4–6 several other solvents were screened resulting in improved A^3-coupling yields. However, only traces of the desired product were obtained. Therefore, we continued our screening with the aprotic polar solvent DMF resulting in an increased yield as shown Table 2 in Entry 7. The omission of 15-crown-5 did not result in a decreased yield presented in Table 2 in Entry 8. In Table 2, Entry 9 performing the reaction at higher temperatures did not further improve the outcome. Applying microwave heating in Table 2 in Entry 10 resulted in only 10% yield of the desired product.

Table 2. Optimisation of the azidation-cyclisation reaction conditions.[a]

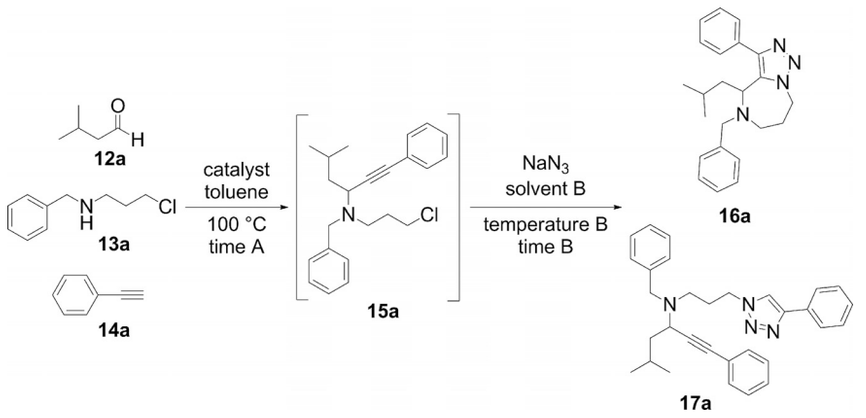
Entry	Temp. [°C]	Solvent	Additive (equiv.)	Time [h]	Yield [%][b]
1	120	DMSO	–	16	40
2	120	DMSO	15-crown-5 (2.5)	16	50
3	120	DMSO	15-crown-5 (2.5)	24	60
4	120	toluene	15-crown-5 (2.5)	16	traces[c]
5	120	ACN	15-crown-5 (2.5)	16	traces[c]
6	120	EtOH	15-crown-5 (2.5)	16	traces[c]
7	120	DMF	15-crown-5 (2.5)	24	69
8	***120***	***DMF***	**–**	***24***	***68***
9	150	DMF	–	24	70
10	120	DMF	–	1[d]	10

[a] Reaction conditions: **15a** (0.28 mmol) and NaN_3 (0.7 mmol, 2.5 equiv.) in the indicated solvent (1 mL). [b] Isolated yields. [c] Decomposition was observed. [d] The reaction was run under microwave irradiation at 80 W maximum power.

Following the optimization of the separate steps we focused on a possible one-pot reaction. In Entry 1 of Table 3 our initial attempts using 0.9 equiv. of phenylacetylene and 10 mol-% of CuBr as catalyst in DMF at 120 °C for 24 h resulted in the formation of the undesired product **17a**. This is formed by an intermolecular copper(I)-catalysed azide-alkyne cycloaddition (CuAAC) reaction between phenylacetylene and the in situ formed alkyl azide. This side reaction might be faster than the thermal intramolecular cycloaddition. Therefore, we evaluated a stepwise one-pot approach by first performing the A^3-coupling and subsequently adding NaN_3 together with a suitable co-solvent for the azidation-cyclisation tandem reaction. We started screening solvents for the second step and again found DMF as best suitable solvent in Table 3 in Entries 2–5. Changing the catalyst for the A^3-coupling to other copper sources resulted in decreased yields as given in Table 3 in Entries 6–8. Performing the A^3-coupling under microwave heating for 45 min resulted in a yield comparable to the one obtained under conventional heating conditions, which can be seen in Table 3 in Entry 9. As expected, reducing the catalyst loading resulted in a significantly decreased yield as presented in Table 3 in Entry 10. When attempting to perform both reaction steps under microwave heating in Entry 11 of Table 3 we obtained only trace amounts of desired product **16a** together with unreacted propargylamine **15a**. Performing the second step at a lower temperature resulted in a significantly reduced yield as shown in Table 3 in Entry 12. Upon running this reaction step for a prolonged time or at a higher temperature the yields decreased notably in Table 3 in Entries 13 and 14, respectively. However, reducing the reaction time and increasing the temperatures of the second step in Table 3, Entry 15 resulted in similar yields as obtained in Table 3, Entries 2 and 9. Consequently, the optimal conditions for the sequential two-step reaction are: (1) A^3-coupling reaction at 100 °C for 3 h under conventional or 45 min under microwave heating with CuBr (10 mol-%) as catalyst; (2) addition of 2.5 equiv. of NaN_3 in DMF as solvent and 24 h under conventional heating at 120 °C (Table 3, Entry 2 and Entry 9). The structure of product **16a** was unambiguously established by X-ray diffraction analysis.[14]

Having the optimal conditions at hand we started exploring the scope of the reaction. A small library of 5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-*a*]diazepines **16** was generated. In R^1 position of the chloropropylamines **13** the reaction tolerates electron-rich and electron-poor benzylic substituents as shown in Table 4 in Entries 1–6 and 11–23. The reaction also gave good yields with an isobutyl substituent on the amine in Table 1 in Entries 7–9. In case of aliphatic aldehydes in R^2 position good to moderate yields were obtained as depicted in Table 4 in Entries 1–9, 11–17 and 19–23. However, in Entries 10 and 18 of Table 4, with aromatic aldehydes the yields dropped significantly. The lower yields

Table 3. Optimisation of the one-pot reaction conditions.[a]

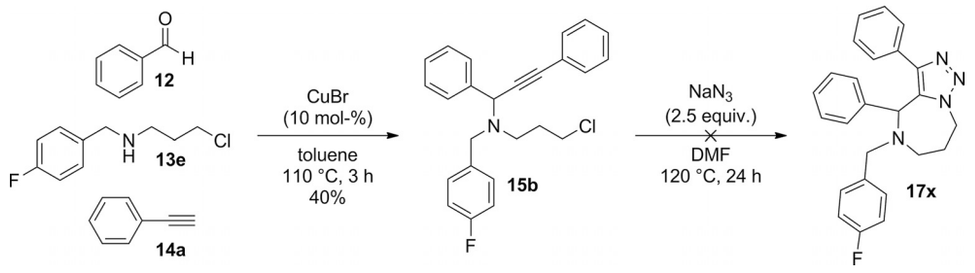


Entry	Catalyst (mol-%)	Time A	Temp. B [°C]	Solvent B	Time B [h]	Yield [%][b]
1[c]	CuBr (10)	–	120	DMF	24	0[d]
2	CuBr (10)	3 h	120	DMF	24	57
3	CuBr (10)	3 h	120	DMA	24	traces[e]
4	CuBr (10)	3 h	120	NMP	24	traces[e]
5	CuBr (10)	3 h	120	DMSO	24	55
6	CuCl (10)	3 h	120	DMF	24	40
7	CuI (10)	3 h	120	DMF	24	38
8	CuOTf (10)	3 h	120	DMF	24	traces[e]
9	CuBr (10)	45 min[f]	120	DMF	24	54
10	CuBr (5)	45 min[f]	120	DMF	24	35
11	CuBr (5)	45 min[f]	120	DMF	4[c]	traces[e]
12	CuBr (10)	3 h	100	DMF	24	22
13	CuBr (10)	3 h	120	DMF	32	48
14	CuBr (10)	3 h	150	DMF	24	45
15	CuBr (10)	3 h	150	DMF	16	56

[a] Reaction conditions: **13a** (0.55 mmol, 1.0 equiv.), 3-methylbutyraldehyde (**12a**) (0.65 mmol, 1.2 equiv.), phenylacetylene (**14a**) (0.5 mmol, 0.9 equiv.) in toluene (0.25 mL) at 100 °C for the indicated time A; then NaN_3 (1.250 mmol, 2.5 equiv.) and the indicated solvent B (1.5 mL) were added, and the mixture was kept at the indicated temperature B for time B. [b] Isolated yields. [c] All reagents of both steps were added together. [d] Product **17a** was isolated. [e] Decomposition was observed. [f] The reaction was run under microwave irradiation at 80 W maximum power.

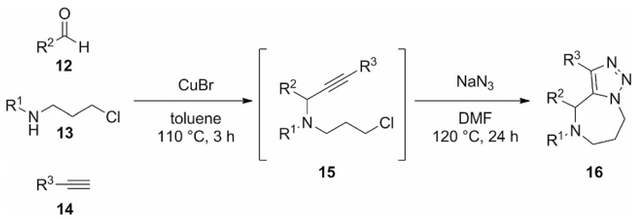
can be attributed to a reduced conversion of the A^3-coupling reaction in case of aromatic aldehydes. Aromatic acetylene substituents in R^3 position resulted in moderate to good yields as given in Table 4 in Entries 1–3, 5–8, 11–12, 14, 16, 17, 19, 20, 22 and 23, while aliphatic substituents in general led to reduced yields compared with aromatic substituents shown in Table 4 in entries 4, 9, 10, 15, 18 and 21. However, in Table 4, Entry 24 attempting the reaction with sterically demanding substituents on all three positions did not result in the formation of the desired product.

In order to determine the reason for the unsuccessful synthesis of **16x** we decided to perform the reaction stepwise. The A^3-coupling resulted in the desired propargylamines **15b** with a yield of 40%. When attempting the subsequent azidation-cyclisation with the isolated product **15b**, we could not find a trace of the desired triazolodiazepine **16x** (Scheme 4). This might be attributed to steric hindrance in the triazolodiazepine disfavouring its formation similar to our previous observations in the synthesis of triazolobenzodiazepines.[10f]



Scheme 4. Attempted two-step synthesis of triazolodiazepine **16x**.

Table 4. Scope and limitations of the reaction.[a]



Entry	Product	R^1	R^2	R^3	Yield [%][b]
1	**16a**	Bn	*i*Bu	Ph	58
2	**16b**	PMB[c]	*i*Bu	Ph	47
3	**16c**	PMB[c]	*i*Pr	Ph	45
4	**16d**	PMB[c]	*i*Bu	Pr	30
5	**16e**	PMB[c]	*i*Bu	4-fluorophenyl	46
6	**16f**	2,4-dimethoxybenzyl	*i*Bu	Ph	68
7	**16g**	*i*Bu	*i*Bu	Ph	67
8	**16h**	*i*Bu	Bu	*p*-tolyl	71
9	**16i**	*i*Bu	*i*Bu	cyclopropyl	59
10	**16j**	*i*Bu	Ph	cyclopropyl	24
11	**16k**	Bn	*i*Pr	Ph	56
12	**16l**	Bn	Bu	*p*-tolyl	71
13	**16m**	Bn	Bu	cyclopropyl	59
14	**16n**	PMB[c]	*i*Bu	PMP[d]	54
15	**16o**	PMB[c]	Bu	cyclopropyl	41
16	**16p**	PMB[c]	cyclohexyl	Ph	52
17	**16q**	PMB[c]	Bu	4-butylphenyl	56
18	**16r**	PMB[c]	Ph	cyclopropyl	27
19	**16s**	4-fluorobenzyl	*i*Bu	Ph	71
20	**16t**	4-fluorobenzyl	Bu	*p*-tolyl	68
21	**16u**	4-fluorobenzyl	Bu	cyclopropyl	58
22	**16v**	4-fluorobenzyl	cyclohexyl	Ph	77
23	**16w**	4-fluorobenzyl	Bu	4-butylphenyl	69
24	**16x**	4-fluorobenzyl	Ph	Ph	–[e]

[a] Reaction conditions: **10** (0.55 mmol, 1.0 equiv.), aldehyde (0.65 mmol, 1.2 equiv.) acetylene (0.5 mmol, 0.9 equiv.) and CuBr (10 mol-%) in toluene (0.25 mL) at 100 °C for 3 h; then NaN_3 (1.25 mmol, 2.5 equiv.) and DMF (1.5 mL) were added, and the mixture was stirred at 120 °C for 24 h. [b] Isolated yields. [c] PMB = *para*-methoxybenzyl. [d] PMP = *para*-methoxyphenyl. [e] Decomposition was observed, and no product could be isolated.

Conclusions

We developed a novel one-pot two-step procedure for the synthesis of 5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-*a*]diazepines. This strategy allows the construction of novel biologically active scaffolds from readily available starting materials. The biological activity of the new triazolodiazepines **17** is currently under investigation.

Experimental Section

General Procedure for the Synthesis of 5,6,7,8-Tetrahydro-4*H*-[1,2,3]triazolo[1,5-*a*][1,4]diazepines 16: 3-Chloropropylamine (**11**) (1 equiv.), aldehyde (1.2 equiv.), acetylene (0.9 equiv.) and CuBr (10 mol-%) were loaded into a screw-cap vial and dissolved in toluene (0.25 mL). The mixture was heated at 100 °C for 3 h. After cooling to room temp., NaN_3 (2.5 equiv.) and DMF (1.5 mL) were added. The reaction mixture was heated at 120 °C for 24 h. After completion, the crude mixture was poured into water (15 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (heptane/EtOAc) to afford triazolodiazepine **16**.

Supporting Information (see footnote on the first page of this article): Experimental procedures, crystallographic information, spectroscopic data and copies of the ^1H and ^{13}C NMR spectra.

Acknowledgments

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[14] See Supporting Information.

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