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Reactivity Control in the Addition of *N*,*N*′-Dialkylated 1,*n*-Diamines to Activated Skipped Diynes: Synthesis of Fused Bicyclic 1,4-Diazepanes and 1,5-Diazocanes

Sara López-Tosco,[a] David Tejedor,*[a] Javier González-Platas,[b] and Fernando García-Tellado*[a]

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A metal-free domino reaction for the synthesis of a new family of fused bicyclic 1,4-diazepanes and 1,5-diazocanes has been developed. The reaction involves the use of *N*,*N*′-dialkylated 1,*n*-diamines as the nitrogen source, through-space orbital interactions between the two nitrogen atoms as the reactivity director element, and an activated skipped diyne as the reactive platform. A key Morita–Baylis–Hillman-like reaction allows the formation of 1,4-diazepanes and 1,5-diazocanes (medium-sized diazoheterocycles). These structures incorporate a 1,*n*-diazocycle fused to a γ-butenolide ring and different functionalities to be used as convenient handles for further complexity generation. The good efficiency of this reaction and its simple experimental protocol make this process an excellent candidate for the fast construction of structure-focused libraries based on this fused bicyclic motif.

Introduction

The direct aza-Michael addition of amines (primary and secondary) onto activated alkynes in the absence of a catalyst is a favored reaction.[1] In this context, it would be possible to react 1,*n*-diamines with double Michael acceptors to generate diazoheterocycles with a size that would depend on the nature of the diamine. 1,4-Diazepanes constitute valuable chemical scaffolds[2] and they are usually synthesized by the reaction of 1,2-diamines or 1,2-bis(sulfonamide)s (or their anions) with 1,3-dihalides,[3] 1,3-dicarbonyl compounds and derivatives,[4] and α,β-unsaturated (or β-halogenated) carbonyl compounds.[5] Activated skipped diynes **1**[6] constitute an exceptional example of densely functionalized scaffolds with a pluripotent reactivity profile (pluripotency refers to the property of expressing more than one chemical outcome) (Figure 1). Recent reports from our group have shown how these platforms can be selectively transformed into polysubstituted pyrroles **2**,[7] pyrazoles **3**,[8] 1,4-diazepane derivatives **4**,[8] polyfunctionalized cyclohexadienones **5**,[9] and aromatic scaffolds **6**[9] when they are made to react with primary amines, hydrazines, 1,2-diamines, and secondary amines, respectively. In this communication, we report on the synthesis of a novel family of fused bicyclic compounds **8** featuring a 1,*n*-diazocyclic core joined to a biologically relevant butenolide motif by an unprecedented reaction of *N*,*N*′-dialkyldiamines **7** with tertiary skipped diynes **1**. The mechanism of this reaction involves a Morita–Baylis–Hillman-like reaction, which is based on through-space nitrogen–nitrogen orbital interactions.

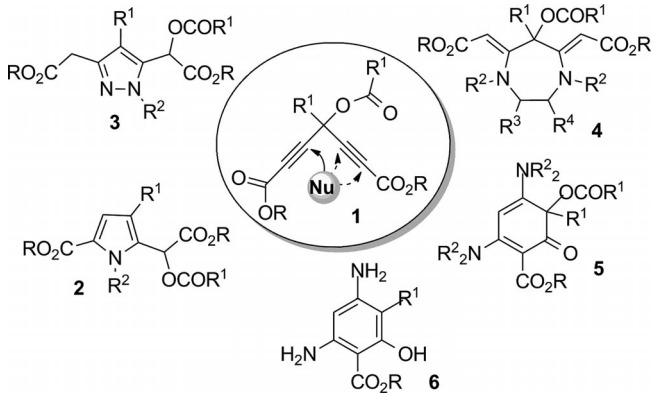

Figure 1. Nucleophilic addition vs. reactivity profile of activated skipped diynes**1**.

Results and Discussion

In our earlier report,[8] we showed that the reaction of *N*,*N*′-dimethylethane-1,2-diamine (**7a**) with skipped diyne

[a] Instituto de Productos Naturales y Agrobiología, Departamento de Química Biológica y Biotecnología, Consejo Superior de Investigaciones Científicas, Astrofísico Francisco Sánchez 3, 38206 La Laguna, Tenerife, Spain
Fax: +34-922260135
E-mail: dtejedor@ipna.csic.es
fgarcia@ipna.csic.es
[b] (Crystallographer) Servicio de Difracción de Rayos X, Departamento de Física Fundamental II. Universidad de La Laguna
Avda. Astrofísico Francisco Sánchez 2, 38204 La Laguna, Tenerife, Spain

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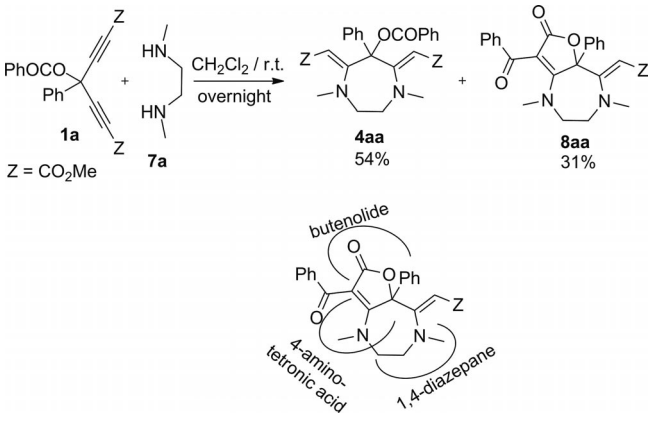
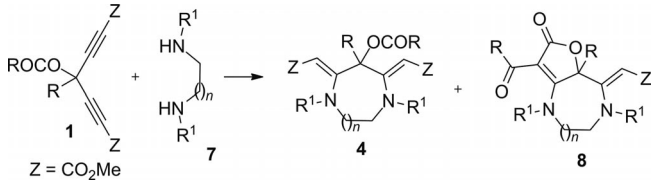
1a afforded expected polysubstituted 1,4-diazepane **4aa** (*Z,Z* isomer, 54% yield), accompanied by a significant amount of a secondary product, which has now been identified as fused bicyclic 1,4-diazepane **8aa** (31%; Scheme 1; Table 1, Entry 1). The structure of this secondary compound, which reveals a higher structural complexity than that expected for a sequential double aza-Michael addition onto the diyne, represents an unexpected and novel chemical outcome for the array of functionalities present in skipped diyne **1a**. From a biological (pharmacological) point of view, this novel structure incorporates relevant pharmacophore motifs; that is, a butenolide ring,[10] a 4-aminotetronic acid,[11] and a 1,4-diazepane ring.[12] On the other hand, from a chemical point of view, the structure accommodates a high functional density on a minimal skeletal connectivity, supporting a reactivity profile steered by the α-benzoyl-substituted butenolide ring and the two chemically differentiated conjugated *N*-methyl enamines. Prompted by the attractive pharmacological and chemical profile of this structure and its unprecedented chemical origin, we undertook the study of this novel reaction and its possible preparative use (Table 1).



Scheme 1. Reaction of activated skipped diyne **1a** and *N*,*N*′-dimethylethane-1,2-diamine (**7a**). Structure and properties of fused bicycle **8aa**.

With regard to the diamine component, the chemical outcome of the reaction was sensitive to steric and electronic factors. Thus, whereas **7a** afforded a mixture of products **4aa/8aa** in a ratio of 1.75:1.0 in a good combined yield (85%), the more sterically demanding *N*,*N*′-dibenzylethane-1,2-diamine (**7b**) rendered a mixture of **4ab/8ab** in a reversed ratio of 0.72:1.0 while maintaining the efficiency (81% combined yield; Table 1, Entries 1 & 2). On the other hand, electron-poor amines (aromatic or amides) did not give the desired compounds (data not shown). Because the reaction constructs fused bicycles, we expected an entropic influence from the size of the diamine linker on the efficiency and chemical outcome of the reaction.[13] Indeed, when the chain linking the two nitrogen atoms was increased by one unit (1,3-diamines), the reaction exclusively afforded the corresponding fused bicyclic 1,5-diazocane derivatives (Table 1, Entries 3–6). Remarkably, the steric environment surrounding the two amine atoms showed a large influence on the efficiency of the reaction. Thus, whereas *N*,*N*′-dimethylpropane-1,3-diamine (**7c**) afforded corresponding product **8ac**[14] in 61% yield (Table 1, Entry 3), homologous diamine **7d** delivered corresponding product **8ad** in a low 10% yield (Table 1, Entry 4). Further increase in the diamine chain resulted in a severe drop in the yield of corresponding fused derivative **8ae** (3% yield; Table 1, Entry 7).

Table 1. Reaction of activated skipped diynes **1** and monosubstituted 1,*n*-diamines **7**.[a]



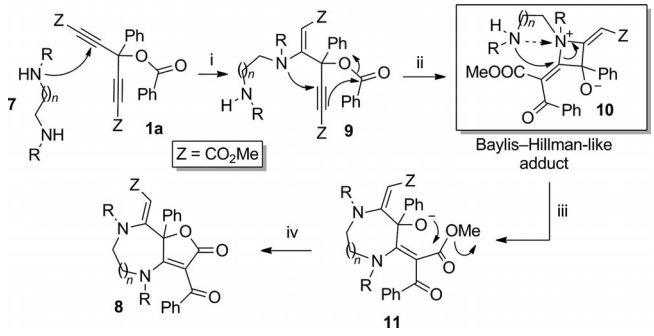
Entry	Ar		*n*	R		Yield [%][b]	
						4	**8**
1	Ph	**1a**	1	Me	**7a**	**4aa** (54)	**8aa** (31)
2	Ph	**1a**	1	Bn	**7b**	**4ab** (34)	**8ab** (47)
3	Ph	**1a**	2	Me	**7c**	**4ac** (0)	**8ac** (61)
4	Ph	**1a**	2	Bn	**7d**	**4ad** (0)	**8ad** (10)
5	4-ClPh	**1b**	2	Me	**7c**	**4bc** (0)	**8bc** (59)
6	4-MePh	**1c**	2	Me	**7c**	**4cc** (0)	**8cc** (60)
7	Ph	**1a**	3	Bn	**7e**	**4ae** (0)	**8ae** (3)

[a] See the Experimental Section for reaction conditions. [b] Isolated yield.

The scope with regard to the diyne derivative was screened by using derivatives **1a**–**c**, which feature three electronically different aromatic rings at the diyne tertiary position and on the ester functionality. As expected, all of them expressed the same reactivity pattern with similar chemical efficiencies (Table 1, Entries 3, 5, and 6).

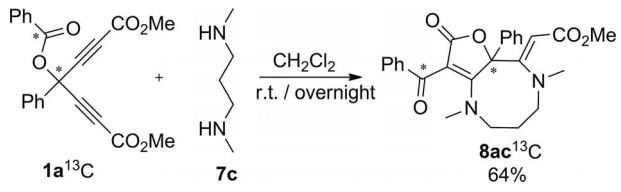
The mechanism for the formation of these fused bicycles is not straightforward. Our proposed mechanism is outlined in Scheme 2. The aza-Michael addition of one amine onto the diyne unit affords enamine intermediate **9** (step i), which cyclizes to give intermediate azetidinium cation **10** (step iii). This cyclization is assisted by through-space orbital interactions with the second nitrogen atom (in the same manner as the two nitrogen atoms interact in the 1,4-diazabicyclo[2.2.2]octane molecule).[15] This cyclization follows a Morita–Baylis–Hillman (MBH)-type reactivity pattern,[16] delivering MBH-adduct-like intermediate **10**,[17,18] which serves as a convenient template for the next cyclization step (step iv). Observe that the formation of **10** allows the generation of eight-membered cycle **11** ($n = 2$), which is not possible from a direct double aza-Michael reaction of the diamine and the diyne. Likewise, the formation of seven-membered cycle **11** ($n = 1$) competes with the formation of corresponding 1,4-diazepane derivative **4**, which is kinetically favored (step ii). This fact outlines the strong electronic influence that the amine nitrogen atom exercises on the reactivity of the enamine nitrogen atom. It is able to competitively overcome the low kinetic barrier needed for

the direct double aza-Michael addition. It should also be noted that, as a consequence of the reduction on the molecular volume produced when enamine **9** forms azetidinium cation **10**, the steric effects exercised by the two amine substituents bring out the reactivity restraints of the molecular system. It is clearly reflected in the data of Table 1, which shows a drop in the yield of fused bicyclic derivative **8** when the methyl substituents are changed by the more sterically demanding benzyl groups. This fact also explains the observed reversed ratio of monocycle **4** to bicycle **8** in the reaction of **7b** with diyne **1a** (Table 1, Entries 1 & 2). Finally, the lactone ring is generated from the intramolecular reaction of the alkoxide ion and the methyl ester with the loss of MeOH (step v).



Scheme 2. Mechanistic proposal for the formation of fused bicyclic structure **8**. Reactions: (i,ii) aza-Michael; (iii) aza-Michael/Baylis–Hillman-like; (iii) aza-addition/elimination, and (iv) lactonization.

The mechanistic hypothesis was further confirmed by ^{13}C-isotopic enrichment NMR experiments (Scheme 3). When skipped diyne **1a** marked with ^{13}C (**1a**^{13}C) was treated with diamine **7c**, corresponding doubly labeled product **8ac**^{13}C was obtained (64% yield). The ^{13}C NMR spectrum showed an increased singlet for the ketone signal (Figure 2), information that corroborates that this carbonyl group comes from the tertiary benzoate group, which confirms the proposed reaction pathway outlined in Scheme 2.



Scheme 3. ^{13}C-isotopic enrichment NMR experiment.

The formation of these fused bicyclic structures expresses a new reactivity profile of skipped diynes **1** when they are made to react with *N*,*N*′-dialkylated 1,*n*-diamines. This reactive profile is elicited by secondary diamines that can exercise a measurable 1–4, 1–5, or 1–6 N→N through-space electronic interaction, which allows a template effect that biases the formation of the otherwise kinetically disfavored eight-membered ring of fused 1,5-diazocanes **8** (*n* = 2).

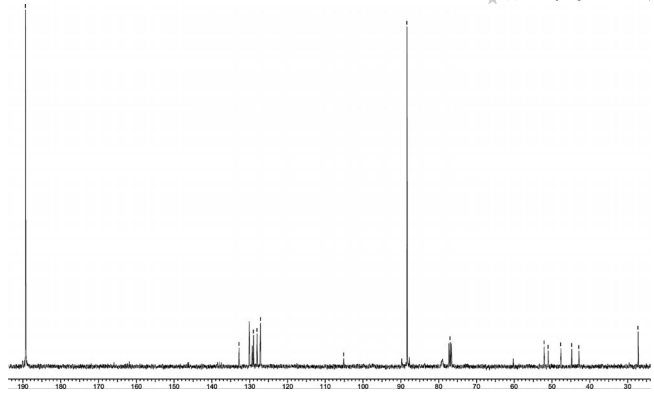


Figure 2. ^{13}C NMR spectrum of **8ac**^{13}C.

Conclusions

In summary, we have developed a novel metal-free protocol for the synthesis of a new family of fused bicyclic structures featuring a skeletal connectivity based on 3,4,5,5a-tetrahydro-1*H*-furo[3,2-*e*][1,4]diazepin-7(2*H*)-one (**8**, *n* = 1) or a 5,6,7,8,9,9a-hexahydrofuro[3,2-*b*][1,5]diazocin-2(4*H*)-one (**8**, *n* = 2). These structures incorporate a fused 1,*n*-diazocycle to a γ-butenolide ring and different chemical functionalities to be used as convenient handles for further complexity generation (one aroyl group attached to the α-position of the butenolide ring and two chemically differentiated conjugated enamine units). In addition, these structures feature an array of pharmacologically relevant structural motives (γ-butenolide ring, 1,*n*-diazocycle, and 4-aza-tetronic acid). They are fast and directly assembled from tertiary skipped diynes and *N*,*N*′-dialkylated 1,*n*-diamines by a domino reaction involving a MBH-like reaction. This procedure uses *N*,*N*′-dialkylated 1,*n*-diamines as the nitrogen source, through-space orbital interactions between the two nitrogen atoms as the reactivity director element, and a diversely functionalized activated skipped diyne as the reactive platform. The length of the alkyl chain of the diamine determines the fate of the cyclization reaction and, therefore, the outcome of the process. The good efficiency of this reaction and its simple experimental protocol make this process an excellent candidate for the fast construction of structure-focused libraries based on this fused bicyclic motif. These libraries will be used in our ongoing drug-discovery research program.[19] These studies are in progress in our laboratory and they will be reported in due course.

Experimental Section

Representative Procedure for the Synthesis of Fused Bicyclic 1,*n*-Diazocycles: 1,*n*-Diamine **7** (0.55 mmol) was added to a solution of skipped diyne **1** (0.50 mmol) in CH_2Cl_2 (13 mL) at room temperature, and the mixture was stirred overnight. The solvent was removed under reduced pressure, and the products were purified by flash column chromatography (silica gel; EtOAc/CH_2Cl_2, 10:90) to give fused bicyclic 1,*n*-diazocycle **8** and, in cases where there are mixtures, 1,4-diazepanes **4**.

Supporting Information (see footnote on the first page of this article): Synthesis and characterization of fused bicyclic 1,*n*-diazocycles **8**, procedure for the synthesis of **8ac**^{13}C, ^{1}H and ^{13}C NMR spectra of selected compounds, and X-ray crystal structure of **8ac**.

Acknowledgments

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[14] The bicyclic 1,5-diazocane structure was unambiguously confirmed by X-ray crystallographic analysis of derivative **8ac** (see the Supporting Information). CCDC-843724 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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