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Tertiary skipped diynes: a pluripotent building block for the modular and diversity-oriented synthesis of nitrogen heterocycles

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The development of diversity-oriented synthetic methodologies (DOS) to construct libraries of small molecules to explore the chemical space is a current topic in modern organic synthesis.[1] An important challenge of these methodologies is the generation of skeletal diversity. This can be generated using the so-called reagent-based DOS methodology which utilizes different reagents to transform a substrate into an array of products having distinct molecular skeletons.[2] In practice, two main reagent-based strategies are currently used: The *densely functionalized molecule* (different functionalities at the same molecule are sequentially transformed by different reagents) and *the pluripotent functional group* (a same functional group at the molecule is transformed by different reagents in different reactions).[3] The latter approach requires the use of building blocks bearing a functional group or an array of interconnected functional groups featuring a polyvalent reactivity profile. Skipped diynes **1**[4] bearing a quaternary sp^3-center and two conjugated alkyne units constitute an example of such building blocks (Figure 1) (**a**$^{\mathbf{i}}$/**d**$^{\mathbf{i}}$ refers to acceptor/donor properties of position **i**).[5] A recent report from this lab has shown that these diynes are efficient precursors of chain functionalized tetrasubstituted pyrroles **2** via an efficient microwave assisted domino reaction with primary amines (Scheme 1).[6] The necessary pyrrole connectivity is generated from the enamine intermediate **I** via a selective 5-*endo*-dig cyclization reaction (a^2 reactivity; anti-aza-Michael addition) in the form of a transient pyrrolidine intermediate **II** which rearranges to the final pyrrole **2** via a sigmatropic [3,3]-Claisen rearrangement ([d^0+a^2] reactivity). In this communication we report our preliminary results in the use of this C_7 pluripotent array of organic functionalities for the generation of other important N-containing heterocycles. As a proof of concept, we describe herein a convenient approach to the regioselective

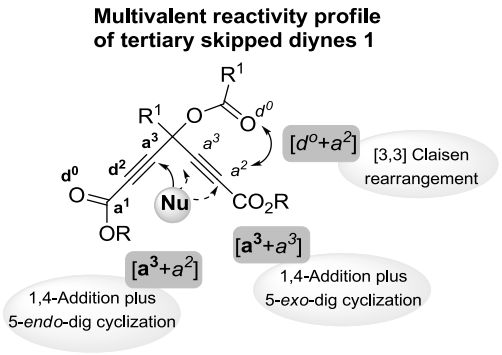
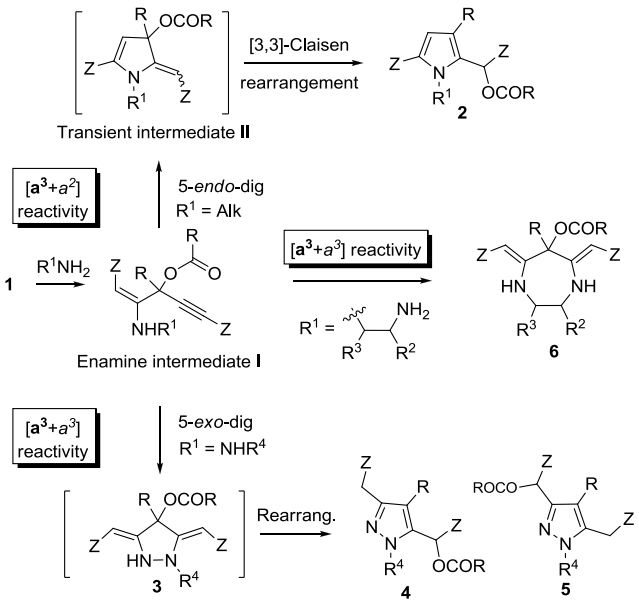


Figure 1. Reactivity profile of tertiary skipped diynes **1**.



Scheme 1.Pluripotent functional array approach to the DOS synthesis of pyrroles **2**, pyrazoles **4** and 1,4-diazepanes **6** from tertiary skipped diynes **1**. Z = CO_2R^5

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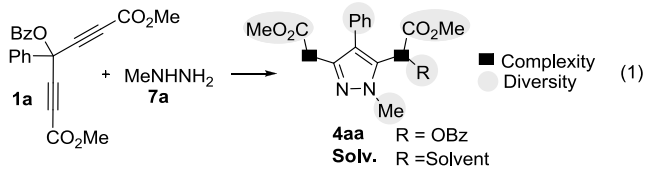
domino synthesis of chain functionalized fully substituted pyrazoles **4** using *N*-substituted hydrazine derivatives (R^2NHNH_2) as nucleophiles (Scheme 1). As an extension of this concept, we have also synthesized 1,4-diazepane derivatives **6** by the use of ethane-1,2-diamine derivatives as N-centered nucleophiles (Scheme 1).

We first focused our efforts on pyrazoles because these heterocycles constitute an important structural motif [7] present in a large number of bioactive molecules spanning a large array of biological and pharmaceutical properties.[8] Traditionally, these heterocyclic units have been assembled by condensation reactions of 1,3-dicarbonyl compounds and hydrazines,[9] or by cycloaddition reactions between alkynes and electron-rich diazo compounds.[10] However, regioselectivity has been a recurrent problem with many of these reactions. In recent years, efficient new processes involving alkyne-containing materials have emerged. These include, among others, Cu-catalyzed domino C–N coupling/hydroamidations, [11] hydrohydrazinations [12] and aza-cyclizations of elaborated substrates.[13] In spite of these advances, the development of general and highly efficient domino metal-free methodologies for the regioselective access to polysubstituted pyrazoles in a modular and diversity-oriented manner from easily accessible starting materials remains a challenge.[14,15]

We initiated our studies with the reaction of commercially available *N*-methyl hydrazine (**7a**) (1.1 equiv) and skipped diyne **1a** (1 equiv) under different experimental conditions [Eq. (1); Table 1). We were pleasant to observe that the microwave irradiation of a solution of **7a** and **1a** in tert-butanol (technical grade; 100 watt, 100 ºC, closed vessel) delivered pyrazole **4aa** in short time and excellent yield (30 min, 92%) (entry 5) accompanied with a small amount (4%) of the solvolysis product (**Solv**.; R = *t*BuO). Other assayed conditions also afforded product **4aa** but with lower efficiency and/or longer reaction times (entries 1-8).



(1)

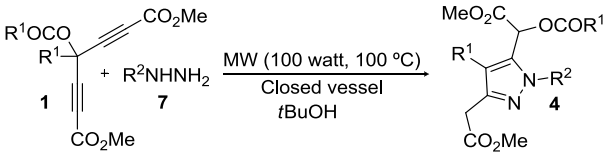
Table 1. Reaction of skipped diyne **1a** and hydrazine **7a**.

	Solvent	Δ/MW[a]	Time	**4aa** (%)	**Solv.** (%)
1	$ClCH_2CH_2Cl$	Reflux	4h	77	--
2	$ClCH_2CH_2Cl$	MW	30 min	79	--
3	EtOH	Reflux	4h	87	14
4	*i*PrOH	Reflux	4h	91	8
5	*t*BuOH	Reflux	8h	88	nd[b]
5	*t*BuOH	MW	30 min	92	4
6	"	MW	15 min	81	nd[b]
7	"	MW	1h	91	3
8	F_3CCH_2OH	MW	30 min	86	8

[a] Microwave irradiation: 100 watt, 100ºC, closed vessel.[b] Not detected

Four chemical properties of this reaction deserve to be highlighted: 1) *efficiency*: the domino reaction constructs the pyrazole topology placing a different substituent at each available ring position, in excellent yield and under bench-friendly conditions; 2) *regioselectivity*: pyrazole **4aa** is obtained as the only regioisomer (pyrazole **5** is not detected)(see ESI for details); 3) *chemoselectivity*: products coming either from the double attack of the same nitrogen atom on the diyne system (5-*endo*-dig cyclization)[6] or from a cyclocondensation reaction between the hydrazine and just one of the two acetylenic esters present in the skipped diyne[16] are not observed and 4) *diversity/complexity*: pyrazoles are assembled bearing five points of diversity and one α-acyloxy ester chain placed in the *ortho*-position to the substituted N-atom of the ring. This arrangement should allow the development of selective complexity generating reactions involving both functionalities (e.g., ring formation).

Once the reaction could be standardized, we next studied the scope of this domino reaction with regard to the hydrazine and the diyne (Table 2). In general, the reaction displayed a wide scope with regard to both components. Although the reaction was tolerant with the nature of the substituent at the hydrazine nitrogen, it was observed that aliphatic substituents afforded the corresponding pyrazoles **4** in better yields than the aromatic ones (compare entries 1,3-6 with 2, 8, 9). Whereas *N*-(4-bromophenyl)-hydrazine (**7h**) gave the corresponding pyrazole **4ah** in modest yield (47%, entry 8), *N*-phenylhydrazine (**7b**) and the electron-rich substituted hydrazine **7i** afforded the corresponding pyrazoles **4ab** and **4ai** in good yields (80% and 74%)(entries 2 and 9). Conversely, hydrazines bearing electron-poor aromatic rings (pCF_3-$C_6H_4NNH_2$ and pNO_2-$C_6H_4NNH_2$) or a sulphonate group ($TsNNH_2$) were not reactive enough to participate in this reaction (data not shown). Hydrazines **7d** and **7e** featuring a reactive functionality at the end of the alkyl chain reacted with diyne **1a** in a very chemoselective and efficient manner to yield pyrazoles **4ad**



(2)

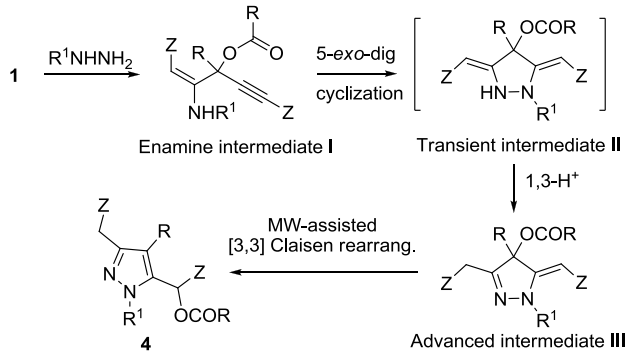
Table 2. Microwave-assisted synthesis of pyrazoles **4**.[a]

	R^1		R^2		t (min)	**4** (%)	
1	Ph	1a	Me	7a	30	4aa	92
2	"	"	Ph	7b	45	4ab	80
3	"	"	Bn[b]	7c	60	4ac	80
4	"	"	$NCCH_2CH_2$	7d	30	4ad	73
5	"	"	$HOCH_2CH_2$	7e	30	4ae	75
6	"	"	*c*Hex[b]	7f	30	4ae	85
7	"	"	H[c]	7g	30	4ag	63
8	"	"	4-BrC_6H_4[b]	7h	180	4ah	47
9	"	"	4-$MeOC_6H_4$[b]	7i	45	4ai	74
10	$pClC_6H_4$	1b	Me	7a	30	4ba	95
11	*p*Tolyl	1c	"	"	30	4ca	99
12	*p*Biphenyl	1d	"	"	30	4da	90
13	$pMeOC_6H_4$	1e	"	"	30	4ea	97
14	$oClC_6H_4$	1f	"	"	30	4fa	88
15	*i*Pr	1g	"	"	60[d]	4ga	95
16	*c*Hex	1h	"	"	60[d]	4ha	97

[a] Diyne (0.5 mmol), hydrazine (0.55 mmol), *t*BuOH (5 mL), MW (100 watt, 100ºC), closed vessel. [b] Hydrazine was used in the form of its hydrochloride salt. Reaction was performed in the presence of NaOAc (3.3 eq). [c] 1.0 M in THF. [d] 300 watt; 150 ºC.

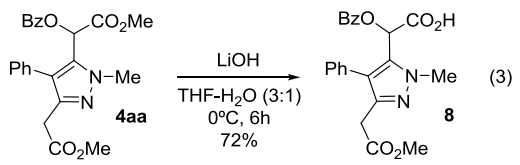
and **4ae** in very good yields, with the extra functionality untouched (entries 4 and 5). These extra functionalities could be convenient handles for further generation of molecular complexity. Remarkably, simple hydrazine **7g** reacted with diyne **1a** in a very efficiently manner to construct the trisubstituted pyrazole **4ag** in good yield (63 %, entry 7). The diyne scope was studied using *N*-methylhydrazine **7a** and a set of different substituted tertiary skipped diynes **1a-h** (entries 10-16). In general, the reaction was tolerant with the nature of the substituent at the tertiary sp^3-center. Although both aliphatic and aromatic derivatives generated the corresponding pyrazoles in excellent yields, aliphatic derivatives needed more energetic conditions than their aromatic homologues to deliver the corresponding pyrazoles in good yields (compare entries 10-14 with 15 and 16).

With regard to the mechanism of this domino reaction, a proposal is outlined in Scheme 2. Remarkably, the advanced intermediate **III** could be isolated when reactions were performed at room temperature. Further transformation of this ring into pyrazole **4** via a [3,3]-Claisen rearrangement required heating (microwave activation) to proceed in a reasonable time (See ESI for details). As expected, this transformation constitutes the rate determining step of the domino process.



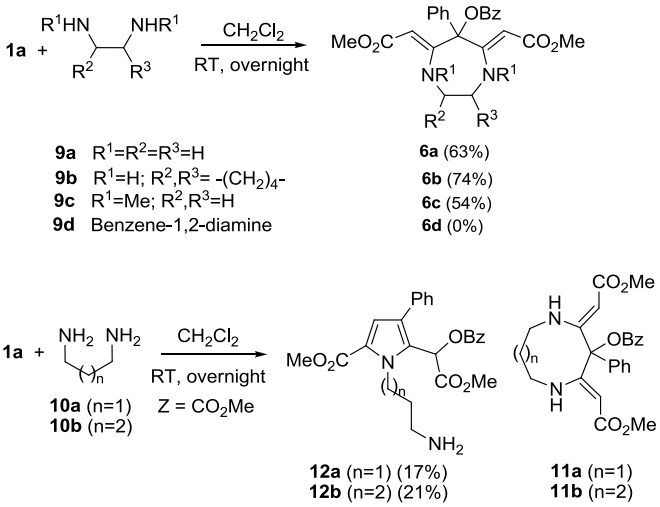
Scheme 2. Mechanistic proposal for the synthesis of pyrazoles **4**. Z = CO_2R^2

It should be noted that the final [3,3]-Claisen rearrangement distinguishes the two ester functionalities by placing an oxygen functionality in the alpha position to one of them. This electronically differentiated ester group should be expected to hydrolyze easier and faster than the other ester group. Hence, the controlled hydrolysis of pyrazole derivative **4aa** (LiOH, THF/H_2O, 0ºC, 6h) [Eq. (3)] proved to be chemoselective, generating monoacid **8** in good yield (72%)(See ESI for details). The free carboxylic acid function at pyrazole **8** gives rise to another point for diversity and/or complexity generation (it can be used as a convenient chemical handle)



(3)

Once the transformation of skipped diynes **1** into pyrazoles was successfully achieved, we next studied the reaction of these diynes with other diamines to gain access to different N-heterocycles. Thus, the reaction of diyne **1a** with 1,2-substituted ethane-1,2-diamines **9a-c** afforded 1,4-diazepane derivatives **6a-c** in good yields and stereoselectivity (*Z,Z*-isomer)[17](See ESI for details), via two consecutive and energetically favoured aza-Michael additions, the latter being a 7-*exo*-dig cyclization process (Scheme 3). The 1,4-diazepane core[18] constitutes a biological valuable scaffold[19] with interesting applications as surrogate of the biologically relevant piperazine ring (homopiperazines).[20] Surprisingly, benzene-1,2-diamine (**9d)** featuring two aromatic amines did not give the corresponding bicyclic 1,4-diazepane **6d**, affording an unresolved mixture of unidentified compounds. Remarkably, the reaction of propane-1,3-diamine (**10a)** with diyne **1a** under these conditions did not afford the corresponding 1,5-diazocane **11a**, but it generated the *N*-substituted pyrrole **12a** (12%; not optimized yield). This result mirrors the inherent energy differences between 5-*endo*-dig (favoured) and 8-*exo*-dig (unfavoured) cyclizations. A similar result was obtained when butane-1,4-diamine (**10b**) was reacted with diyne **1a** under the same reaction conditions (Scheme 3). Instead of the expected 1,5-diazonane derivative **11b** resulting from an allowed *9-exo*-dig cyclization process, pyrrol **12b** was obtained as the major compound (21%; not optimized yield). These studies show that the length of the alkyl chain of the diamine determines the fate of the cyclization reaction, and therefore the outcome of the process. Only 1,2-diamines react with diyne **1a** using their two nitrogen atoms to afford 1,4-diazepane derivatives **6** via two kinetically allowed aza-Michael additions. The rest of the 1,n-diamines react as simple monoamines affording the corresponding *N*-(aminoalkyl)-pyrrole derivatives **12** via a well established domino mechanism.[6]



Scheme 3. Reaction of skipped diyne **1a** and alkane 1,n-diamines**.**

In summary, we have shown that the tertiary skipped diyne motif **1** is a pluripotent functional array which can be conveniently used to generate skeletal diversity. Different N-heterocyclic cores can be constructed by reaction of this motif with different N-centered nucleophiles, via different reaction pathways involving the same set of functionalities.

Experimental Section

Representative procedure for the microwave-assisted synthesis of pyrazoles (4aa-4ha). Methylhydrazine **7a** (0.55 mmol) was added to a solution of diyne **1a** (0.50 mmol) in *t*-Butanol (4 ml). The reaction mixture was placed in a microwave-special closed vial and the solution was irradiated for 30 min in a single-mode microwave oven (100 Watt, 100 ºC). After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, n-hexane/EtOAc 40/60) to yield **4aa** (92%). ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 3.61 (d, 1H, *J* = 16.9 Hz), 3.63 (s, 3H), 3.66 (d, ^3J(H,H) = 16.4 Hz, 1H), 3.71 (s, 3H), 4.04 (s, 3H), 6.38 (s, 1H), 7.32-7.45 (m, 7H), 7.55-7.60 (m, 1H), 7.99 (d, ^3J(H,H) = 7.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ = 32.5, 38.0, 52.0, 53.0, 65.5, 123.7, 127.6, 128.5, 128.6, 128.7, 129.9, 130.0, 131.3, 132.4, 133.7, 142.7, 165.0, 167.2, 171.0 ppm; IR ($CHCl_3$): ν = 3000.3, 3028.2, 2955.9, 1733.3, 1445.8, 1334.9, 1266.5, 1237.7 1175.0, 1099.0 cm^{-1}; MS (70 eV):*m/z* (%): 422 (30) [M+], 317 (20), 259 (6.3), 241 (11), 105 (100), 77 (15); elemental analysis calcd (%) for $C_{23}H_{22}N_2O_6$: C 65.39, H 5.25, N 6.63; found: C 65.38, H 5.28, N 6.43.

Representative procedure for the synthesis of diazepanes (6a-6c). Ethane-1,2-diamine (0.55 mmol) was added to a solution of diyne **1a** (0.50 mmol) in dry CH_2Cl_2 (13 ml) at room temperature. The reaction mixture was stirred overnight. After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, EtOAc / CH_2Cl_2 10/90) to yield **6a** (63%). mp 199.3-199.6 ºC. ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ= 3.53 (s, 6H), 3.57-3.62 (m, 2H), 3.69-3.74 (m, 2H), 4.87 (s, 2H), 7.33-7.39 (m, 3H), 7.47-7.51 (m, 2H), 7.61 (tt, ^3J(H,H) = 7.4, 1.3 Hz, 1H), 7.68-7.70 (m, 2H), 8.09-8.12 (m, 2H), 9.59 (bs, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ= 45.0, 50.3, 84.1, 84.5, 126.3, 128.3, 128.65, 128.69, 129.8, 129.9, 133.7, 141.5, 164.3, 164.9, 171.3 ppm; IR ($CHCl_3$): ν = 1091.2, 1192.8, 1262.6, 1497.3, 1603.8, 1655.3, 1733.7 cm^{-1}; MS (70 eV):*m/z* (%): 436 (23) [M+], 331 (63), 315 (50), 283 (37), 105 (100), 77 (35); elemental analysis calcd (%) for $C_{24}H_{24}N_2O_6$: C 66.04, H 5.54, N 6.42; found: C 66.13, H 5.66, N 6.43.

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Keywords: alkynes • cyclization • domino reactions • pyrazoles • 1,4-diazepanes

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[4] These units are assembled via a tetracomponent A_2BB' reaction manifold involving triethylamine, alkyl propiolates and acid chlorides. D. Tejedor, S. López-Tosco, J. González-Platas, F. García-Tellado, *J. Org. Chem.* **2007**, *72*, 5454-5456. A_2BB' means that the component A is incorporated into the final product twice and in the same manner (A_2) whereas the component B does it in two chemo-differentiated manners (B and B'). For a tutorial about these and related multicomponent reactions, see: D. Tejedor, F. García-Tellado, *Chem. Soc. Rev*. **2007**, *36*, 484-491.

[5] Each alkynoate group holds a polyvalent reactivity profile which is expressed as simple codes **d^0**, **a^1**, **a^2**, **a^3**, **d^2** or combinations of them (letters refer to acceptor/donor properties while numbers refer to position). Each notation (**a^i**, **d^i**) codifies for a particular chemical transformation at this specific position, i.e., **a^1** codifies for 1,2-addition, **a^3** for 1,4-addition, and so on. D. Tejedor, S. López-Tosco, F. Cruz-Acosta, G. Méndez-Abt, F. García-Tellado, *Angew. Chem*. **2009**, *121*, 2124-2131; *Angew. Chem. Int. Ed*. **2009**, *48*, 2090-2098. For a discussion of this nomenclature, see: D. Seebach *Angew. Chem.* **1979**, *91*, 259-278; *Angew. Chem. Int. Ed*. 1979, 18,239-258 .

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[20] For recent examples, see: a) S. Bedürftig, B. Wünsch, *Eur. J. Med. Chem.* **2009**, *44*, 519-525; b) L. P. J. Hoeglund, S. Silver, M. T. Engstroem, H. Salo, A.Tauber, H.-K. Kyyroenen, P. Saarenketo, A.-M Hoffren, K. Kokko, K. Pohjanoksa, *J. Med. Chem.* **2006**, *49*, 6351-6363.

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Entry for the Table of Contents (Please choose one layout only)

Layout 1:

Substrate-based DOS

David Tejedor, Sara López-Tosco, Javier González-Platas and Fernando García-Tellado*……*
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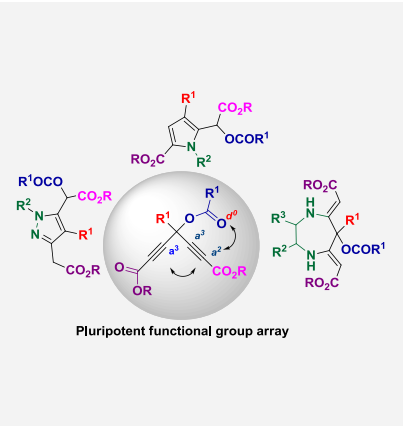
Tertiary skipped diynes: a pluripotent building block for the modular and diversity-oriented synthesis of nitrogen heterocycles



The multivalent reactivity profile of tertiary skipped diynes has been conveniently exploited in the domino and diversity-oriented synthesis of fully substituted pyrazoles and 1,4-diazepanes derivatives. The developed manifold is chemically efficient and simple to operate. In addition, the resulting N-containing heterocycles are obtained in a regio- and chemoselective manner.