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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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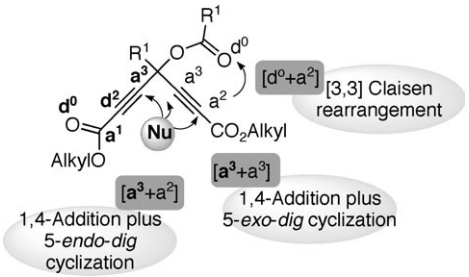
The development of diversity-oriented synthetic (DOS) methodologies to construct libraries of small molecules to explore chemical space is a current topic in modern organic synthesis.[1] An important challenge for these methodologies is the generation of skeletal diversity. This can be generated by using the so-called reagent-based DOS methodology, which utilises different reagents to transform a substrate into an array of products with distinct molecular skeletons.[2] In practice, two main reagent-based strategies are currently used: the densely functionalised molecule (different functionalities in the same molecule are sequentially transformed by different reagents) and the pluripotent functional group (the same functional group in the molecule is transformed by different reagents in different reactions).[3] The latter approach requires the use of building blocks containing a functional group, or an array of interconnected functional groups, featuring a polyvalent reactivity profile. Skipped diynes **1**[4] with a quaternary sp^3 centre and two conjugated alkyne units constitute an example of such building blocks (Scheme 1; $\mathbf{a}^i/\mathbf{d}^i$ refer to acceptor/donor properties of position *i*).[5] A recent report from this lab has shown that these diynes are efficient precursors of chain-functionalised, tetrasubstituted pyrroles **2** by an efficient microwave-assisted domino reaction with primary amines (Scheme 2).[6] The necessary pyrrole connectivity is generated from the enamine intermediate **I** by a selective 5-*endo-dig* cyclisation reaction (a^2 reactivity; anti-aza-Michael addition) via a transient pyrrolidine intermediate **II** that rearranges into the final pyrrole **2** by a sigmatropic [3,3]-Claisen rearrangement ($[d^0+a^2]$ reactivity). Herein, we report our preliminary results on 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 a convenient approach to the regioselective domino synthesis of chain-functionalised, fully substituted pyrazoles **4** by using N-substituted hydrazine derivatives (R^4NHNH_2) as nucleophiles (Scheme 2). As an extension of this concept, we have also synthesised 1,4-diazepane derivatives **6** by using ethane-1,2-diamine derivatives as N-centred nucleophiles (Scheme 2).



Scheme 1. Reactivity profile of tertiary skipped diynes **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 wide 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, regioselec-

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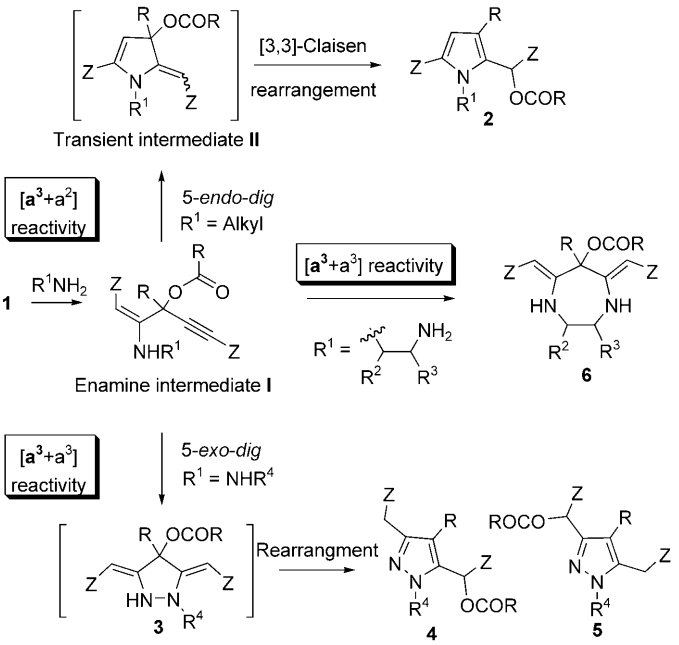


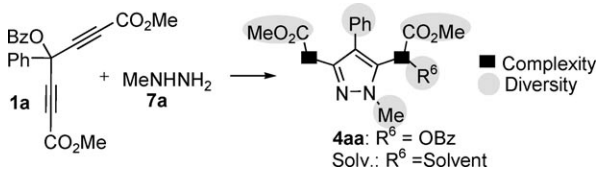
Scheme 2. Pluripotent functional array approach to the diversity-oriented synthesis of pyrroles **2**, pyrazoles **4** and 1,4-diazepanes **6** from tertiary skipped diynes **1**. Z = CO_2R^5.

tivity 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-catalysed domino C–N coupling/hydroamidations,[11] hydrohydrazinations[12] and aza-cyclisations of complex substrates.[13] In spite of these advances, the development of general, highly efficient, metal-free domino methodologies for 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 (Table 1). We were pleased to observe that the microwave irradiation of a solution of **7a** and **1a** in *tert*-butanol (technical grade; 100 W, 100 °C, closed vessel) delivered pyrazole **4aa** in a short time and excellent yield (30 min, 92 %; Table 1, entry 5) accompanied by a small amount (4 %) of the solvolysis product (Solv.; R^6 = *t*BuO). Other assayed conditions also afforded product **4aa**, but with lower efficiency and/or longer reaction times (Table 1).

Four 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 the Supporting Information for details); 3) chemoselectivity: neither products coming from the double attack of the same nitrogen atom on the diyne system (5-*endo-dig* cyclisation)[6] nor those from a cyclocondensation reaction between the hydrazine and just one of the two acetylenic esters present in the skipped diyne[16] are observed and 4) diversity/complexity: pyrazoles are assembled with five points of diversity and one α-acyloxy ester chain placed *ortho* 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).

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

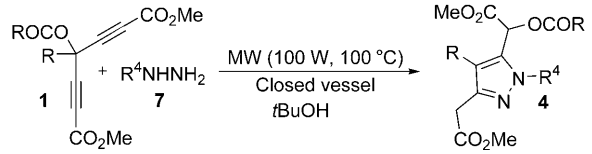


	Solvent	Δ/MW[a]	*t*	**4aa** [%]	Solv. [%]
1	$ClCH_2CH_2Cl$	reflux	4 h	77	nd[b]
2	$ClCH_2CH_2Cl$	MW	30 min	79	nd[b]
3	EtOH	reflux	4 h	87	14
4	*i*PrOH	reflux	4 h	91	8
5	*t*BuOH	reflux	8 h	88	nd[b]
5	*t*BuOH	MW	30 min	92	4
6	*t*BuOH	MW	15 min	81	nd[b]
7	*t*BuOH	MW	1 h	91	3
8	F_3CCH_2OH	MW	30 min	86	8

[a] Microwave irradiation: 100 W, 100 °C, closed vessel. [b] Not detected.

Once the reaction had been standardised, we 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 of the nature of the substituent at the

Table 2. Microwave-assisted synthesis of pyrazoles **4**.

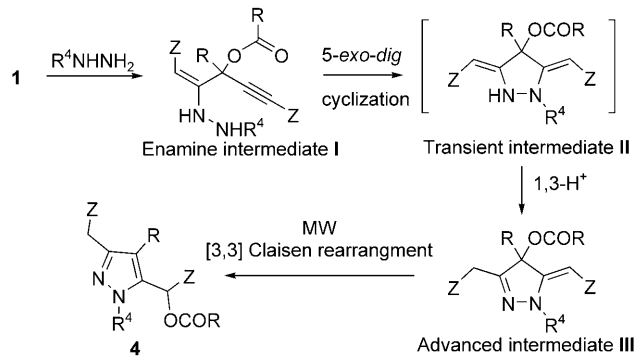


	R	R^4	*t* [min]	Product **4**	Yield [%]
1	Ph (**1a**)	Me (**7a**)	30	**4aa**	92
2	Ph (**1a**)	Ph (**7b**)	45	**4ab**	80
3	Ph (**1a**)	Bn[b,c] (**7c**)	60	**4ac**	80
4	Ph (**1a**)	$NCCH_2CH_2$ (**7d**)	30	**4ad**	73
5	Ph (**1a**)	$HOCH_2CH_2$ (**7e**)	30	**4ae**	75
6	Ph (**1a**)	*c*Hex[b,c] (**7f**)	30	**4ae**	85
7	Ph (**1a**)	H[d] (**7g**)	30	**4ag**	63
8	Ph (**1a**)	4-BrC_6H_4[b] (**7h**)	180	**4ah**	47
9	Ph (**1a**)	4-$MeOC_6H_4$[b] (**7i**)	45	**4ai**	74
10	*p*-ClC_6H_4 (**1b**)	Me (**7a**)	30	**4ba**	95
11	*p*-tolyl (**1c**)	Me (**7a**)	30	**4ca**	99
12	*p*-biphenyl (**1d**)	Me (**7a**)	30	**4da**	90
13	*p*-$MeOC_6H_4$ (**1e**)	Me (**7a**)	30	**4ea**	97
14	*o*-ClC_6H_4 (**1f**)	Me (**7a**)	30	**4fa**	88
15	*i*Pr (**1g**)	Me (**7a**)	60[e]	**4ga**	95
16	*c*Hex (**1h**)	Me (**7a**)	60[e]	**4ha**	97

[a] Diyne (0.5 mmol), hydrazine (0.55 mmol), *t*BuOH (5 mL), MW (100 W, 100 °C), closed vessel. [b] Hydrazine was used in the form of its hydrochloride salt. The reaction was performed in the presence of NaOAc (3.3 equiv). [c] Bn = benzyl, *c*Hex = cyclohexyl. [d] 1.0 M in THF. [e] 300 W; 150 °C.

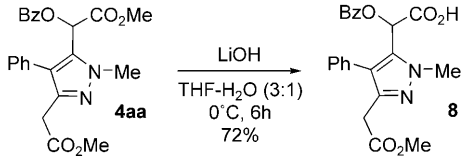
hydrazine nitrogen, it was observed that aliphatic substituents afforded the corresponding pyrazoles **4** in better yields than those with aromatic ones (compare entries 1, 3–6 with entries 2, 8 and 9 in Table 2). Whereas *N*-(4-bromophenyl)-hydrazine (**7h**) gave the corresponding pyrazole **4ah** 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%, respectively; Table 2, entries 2 and 9). Conversely, hydrazines with electron-poor aromatic rings (*p*-$CF_3C_6H_4NNH_2$ and *p*-$NO_2C_6H_4NNH_2$) or a sulfonate 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 chemoselective and efficient manner to yield pyrazoles **4ad** and **4ae** in very good yields, with the extra functionality untouched (Table 2, 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 efficient manner to construct the trisubstituted pyrazole **4ag** in good yield (63%; Table 2, entry 7). The diyne scope was studied by using *N*-methylhydrazine **7a** and a set of substituted tertiary skipped diynes **1a–h** (Table 2, entries 10–16). In general, the reaction was tolerant of the nature of the substituent at the tertiary sp^3 centre. 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 entries 15 and 16 in Table 2).

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



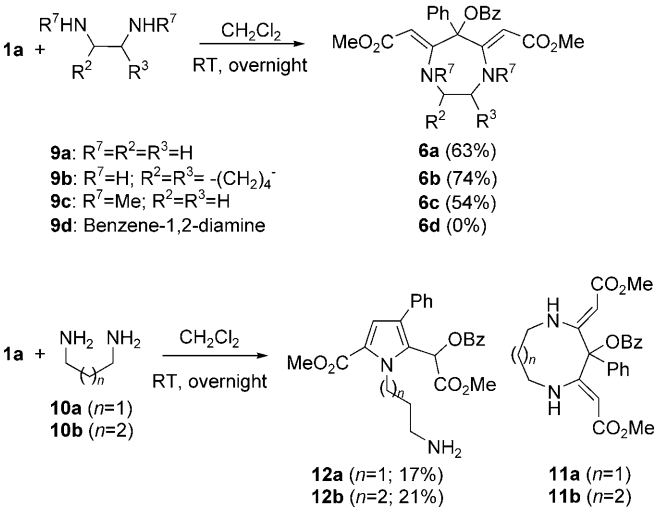
Scheme 3. Mechanistic proposal for the synthesis of pyrazoles **4**. Z = CO_2R^5.

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 be hydrolysed more easily and faster than the other ester group. Hence, controlled hydrolysis of pyrazole derivative **4aa** (LiOH, THF/H_2O, 0 °C, 6 h) (Scheme 4) proved to be chemoselective, generating monoacid **8** in good yield (72%; see the Supporting Information for details). The free carboxylic acid functionality in pyrazole **8** gives rise to another position for the generation of diversity and/or complexity (it can be used as a convenient chemical handle).



Scheme 4. Controlled hydrolysis of pyrazole **4aa**.

Once the transformation of skipped diynes **1** into pyrazoles was successfully achieved, we 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 yield and stereoselectivity (*Z,Z* isomer;[17] see the Supporting Information for details), through two consecutive and energetically favoured aza-Michael additions, the latter being a 7-*exo-dig* cyclisation process (Scheme 5). The 1,4-diazepane core[18] constitutes a biologically valuable scaffold[19] with interesting applications as a surrogate of the biologically relevant piperazine ring (homopiperazines).[20] Surprisingly, benzene-1,2-diamine (**9d**), featuring two aromatic amines, did not give the correspond-



Scheme 5. Reaction of skipped diyne **1a** and alkane 1,*n*-diamines.

ing bicyclic 1,4-diazepane **6d**, affording a mixture of unidentified products. 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 instead it generated the *N*-substituted pyrrole **12a** (12%; not optimised yield). This result mirrors the inherent energy differences between 5-*endo-dig* (favoured) and 8-*exo-dig* (unfavoured) cyclisations. A similar result was obtained when butane-1,4-diamine (**10b**) was treated with diyne **1a** under the same reaction conditions (Scheme 5). Instead of the expected 1,5-diazepane derivative **11b** resulting from an allowed 9-*exo-dig* cyclisation process, pyrrole **12b** was obtained as the major compound (21%; not optimised yield). These studies show that the length of the alkyl chain of the diamine determines the fate of the cyclisation 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** through 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** by a well-established domino mechanism.[6]

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

Experimental Section

Representative procedure for the microwave-assisted synthesis of pyrazoles (4aa–ha): Methylhydrazine **7a** (0.55 mmol) was added to a solution of diyne **1a** (0.50 mmol) in *tert*-butanol (4 mL). The reaction mixture was placed in a special microwave closed vial and the solution was irradiated for 30 min in a single-mode microwave oven (100 W, 100°C). 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, $CDCl_3$, 25°C): δ = 3.61 (d, ^3J(H,H) = 16.9 Hz, 1H), 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 ppm (d, ^3J(H,H) = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): 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–c): Ethane-1,2-diamine **9a** (0.55 mmol) was added to a solution of diyne **1a** (0.5 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°C; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): 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 ppm (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): 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 · diazepanes · domino reactions · pyrazoles

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[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 thereof (the letters refer to acceptor/donor properties, while the numbers refer to the position). Each notation (**a^i**, **d^i**) codes for a particular chemical transformation at this specific position, for example, **a^1** codes 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; *Angew. Chem. Int. Ed.* **1979**, *18*, 239–258.

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